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PCT/GB98/03766

.TENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

MILES, John
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD
ROYAUME-UNI

Date of mailing (day/month/year)
07 September 1999 (07.09.99)

Applicant's or agent's file reference
DUNW/P20111PC

IMPORTANT NOTIFICATION

International application No.
PCT/GB98/03766

International filing date (day/month/year)
15 December 1998 (15.12.98)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

BASSETT, Richard
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 0115 955 2211

Facsimile No.: 0115 955 2201

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address

MILES, John
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 0115 955 2211

Facsimile No.: 0115 955 2201

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Patricia Gonzalez

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 September 1999 (07.09.99)	
International application No. PCT/GB98/03766	**Applicant's or agent's file reference** DUNW/P20111PC
International filing date (day/month/year) 15 December 1998 (15.12.98)	**Priority date** (day/month/year) 16 December 1997 (16.12.97)
Applicant SCHOR, Seth, Lawrence et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   16 July 1999 (16.07.99)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Patricia Gonzalez
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

CORRECTED VERSION*

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, 5/10, 15/63, C07K 14/78, 16/18, C12Q 1/68, G01N 33/574, A61K 38/39

A1

(11) International Publication Number: WO 99/31233

(43) International Publication Date: 24 June 1999 (24.06.99)

(21) International Application Number: PCT/GB98/03766

(22) International Filing Date: 15 December 1998 (15.12.98)

(30) Priority Data:
9726539.1 16 December 1997 (16.12.97) GB

(71) Applicant *(for all designated States except US)*: UNIVERSITY OF DUNDEE [GB/GB]; 11 Perth Road, Dundee DD1 4HN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SCHOR, Seth, Lawrence [GB/GB]; Unit of Cell and Molecular Biology, The Dental School, University of Dundee, Dundee DD1 4HR (GB). SCHOR, Ana, Maria [ES/GB]; Unit of Cell and Molecular Biology, The Dental School, University of Dundee, Dundee DD1 4HR (GB).

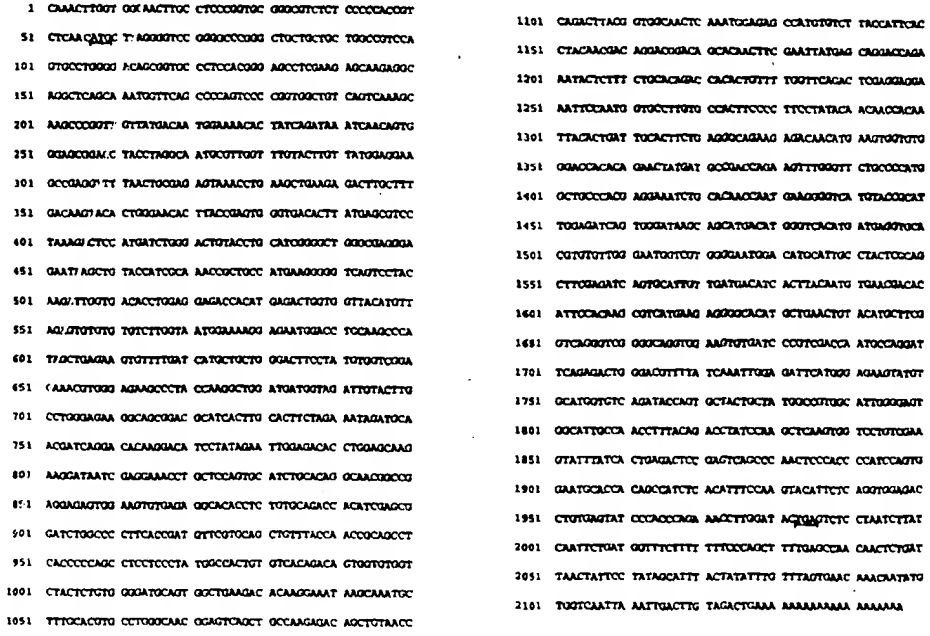
(74) Agent: BASSETT, Richard; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: POLYPEPTIDES, POLYNUCLEOTIDES AND USES THEREOF



(57) Abstract

A recombinant polynucleotide encoding migrating stimulating factor (MSF) or variants or fragments or derivatives or fusions thereof or fusions of said variants or fragments or derivatives. Reagents are disclosed which can distinguish MSF and fibronectin, and which can distinguish polynucleotides which encode MSF or fibronectin. These reagents are believed to be useful in, for example, diagnosing cancer. MSF or variants or fragments or derivatives or fusions thereof, or fusions of said

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: UNIVERSITY OF DUNDEE [GB/GB]; 11 Perth Road, Dundee DD1 4HN (GB).

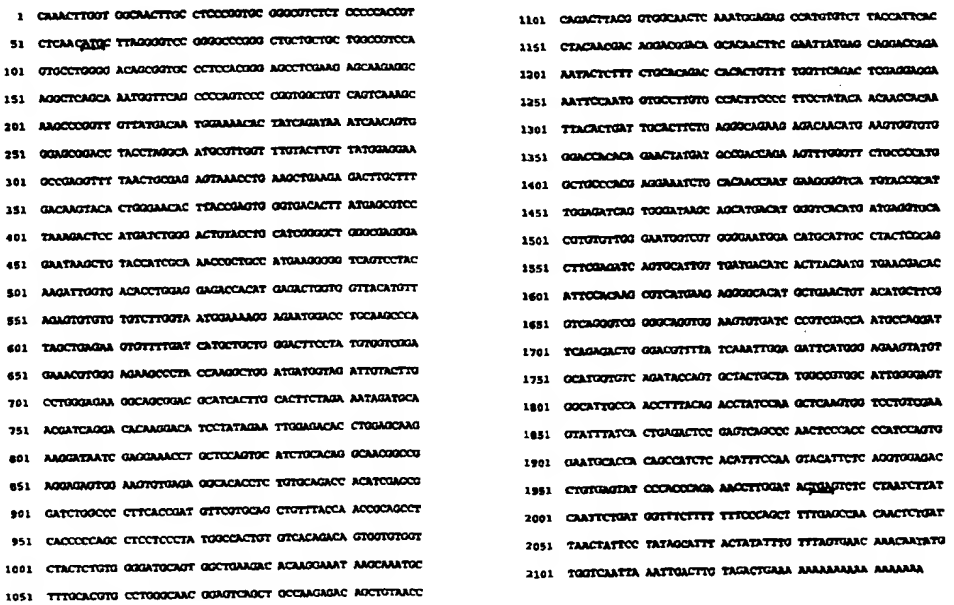
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SCHOR, Seth, Lawrence [GB/GB]; Unit of Cell and Molecular Biology, The Dental School, University of Dundee, Dundee DD1 4HR (GB). SCHOR, Ana, Maria [ES/GB]; Unit of Cell and Molecular Biology, The Dental School, University of Dundee, Dundee DD1 4HR (GB).

(74) Agent: BASSETT, Richard; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: POLYPEPTIDES, POLYNUCLEOTIDES AND USES THEREOF



(57) Abstract

A recombinant polynucleotide encoding migrating stimulating factor (MSF) or variants or fragments or derivatives or fusions thereof or fusions of said variants or fragments or derivatives. Reagents are disclosed which can distinguish MSF and fibronectin, and which can distinguish polynucleotides which encode MSF or fibronectin. These reagents are believed to be useful in, for example, diagnosing cancer. MSF or variants or fragments or derivatives or fusions thereof, or fusions of said variants or fusions or derivatives, are useful in modulating cell migration and in wound healing.

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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/03766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N5/10 C12N15/63 C07K14/78 C07K16/18
C12Q1/68 G01N33/574 A61K38/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 16085 A (ZYMOGENETICS INC) 21 July 1994	1-3, 6-13,27, 29,53-57
A	see abstract; claims	4,5,51, 52
	see page 2, line 30 - page 4, line 8	
A	WO 90 00567 A (CANCER RES CAMPAIGN TECH) 25 January 1990	9-18,25, 27,29, 36-39, 44-57
	see page 1 - page 10	
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 May 1999	07/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ceder, O

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KORNBLIHTT ET AL.: "Human mRNA for fibronectin" EMBL SEQUENCE DATABASE,7 November 1985, XP002103220 HEIDELBERG DE Ac X02761 see the whole document	1-3,6
X	-& KORNBLIHTT ET AL.: "Primary structure of human fibronectin: differential splicing may generate at least 10 polypeptides from a single gene" THE EMBO JOURNAL , vol. 4, no. 7, 1985, pages 1755-1759, XP002051533 see abstract see page 1759, left-hand column	1-3,6, 10-13, 27,29
X	KORNBLIHTT ET AL.: "Human fibronectin precursor" SWISSPROT SEQUENCE DATA BASE,21 July 1986, XP002103221 Ac P02751 see the whole document	10-13, 27,29
X	& KORNBLIHTT ET AL.: "Primary structure of human fibronectin: differential splicing may generate at least 10 polypeptides from a single gene" THE EMBO JOURNAL, vol. 4, no. 7, 1985, pages 1755-1759, XP002051533 see abstract see page 1759, left-hand column	1-3,6, 10-13, 27,29
X	EP 0 207 751 A (DELTA BIOTECHNOLOGY LTD) 7 January 1987 see abstract; claims; figures 2,3 see page 13, line 30 - page 15, line 10	1,3, 6-10,12, 13,27,29
X	"Homo sapiens fibronectin splice form ED-A" PIR1 SEQUENCE DATA BASE,27 November 1985, XP002103253 Ac FNHU see the whole document & DEAN ET AL.: "Cloning and analysis of the promoter region of the human fibronectin gene" PROC. NATL. ACAD. SCI. U.S.A., vol. 84, 1987, pages 1876-1880,	10-13, 27,29
X	EP 0 344 134 A (IST NAZ RIC SUL CANCRO) 29 November 1989 see abstract; figure 1	19-24, 26,28,30

-/--

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 98/03766

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 571 679 A (SEKIGUCHI KIYOTOSHI ET AL) 5 November 1996	14-17, 24,25,27
A	US 5 629 291 A (RUOSLAHTI ERKKI I ET AL) 13 May 1997 see abstract see column 1, line 29 - line 40 see column 1, line 55 - line 57	10,29, 36,47, 48,53-55

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03766

B x I Observations where certain claims were found unsear hable (C ntinuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet PCT/ISA/210

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 98 /03766

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-18, 25, 27, 29, 31, 33 and 36-58 in totality, and 24, 34 and 35 partly

Polynucleotide and polypeptide of migration stimulating factor and their uses, and an antibody reactive with the polypeptide, but not with fibronectin, and the use of the antibody.

2. Claims: 19-23, 26, 28, 30 and 32 in totality, and 24, 34 and 35 partly

An antibody reactive with fibronectin but not with the polypeptide of invention I, and its use.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 98 /03766

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 47-50, 52, 53, 55 and 58 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/03766

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9416085 A	21-07-1994	US 5830700 A	03-11-1998
WO 9000567 A	25-01-1990	EP 0423207 A	24-04-1991
		JP 3505732 T	12-12-1991
EP 0207751 A	07-01-1987	AT 58381 T	15-11-1990
		AU 603059 B	08-11-1990
		AU 5931586 A	08-01-1987
		DK 306386 A	29-12-1986
		FI 862756 A	29-12-1986
		JP 62089699 A	24-04-1987
EP 0344134 A	29-11-1989	AT 100471 T	15-02-1994
		DE 68912403 D	03-03-1994
		DE 68912403 T	11-05-1994
US 5571679 A	05-11-1996	EP 0580859 A	02-02-1994
		WO 9217604 A	15-10-1992
US 5629291 A	13-05-1997	US 5453489 A	26-09-1995
		US 5747452 A	05-05-1998
		US 5837813 A	17-11-1998
		AT 152173 T	15-05-1997
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		CA 2129115 A	05-08-1993
		DE 69310145 D	28-05-1997
		DK 624196 T	03-11-1997
		EP 0624196 A	17-11-1994
		FI 943568 A	29-07-1994
		JP 7506342 T	13-07-1995
		NO 942825 A	29-09-1994
		WO 9315203 A	05-08-1993

POLYPEPTIDES, POLYNUCLEOTIDES AND USES THEREOF

The present invention relates to polypeptides, polynucleotides and uses thereof and in particular to migration stimulating factor (MSF).

MSF has been described previously in the following papers. Schor *et al* (1988) *J. Cell Sci.* **90**: 391-399 shows that foetal and cancer patient fibroblasts produce an autocrine migration stimulating factor not made by normal adult cells. Schor *et al* (1988) *J. Cell Sci.* **90**: 401-407, shows that fibroblasts from cancer patients display a mixture of both foetal and adult phenotypic characteristics. Schor *et al* (1989) *In Vitro* **25**: 737-746 describes a mechanism of action of the migration stimulating factor (MSF) produced by fetal and cancer patient fibroblasts and its effect on hyaluronic acid synthesis. Grey *et al* (1989) *Proc. Natl. Acad. Sci. (USA)* **86**: 2438-2442 describes the purification of the migration stimulating factor produced by fetal and cancer patient fibroblasts but no amino acid sequence information is given. It is suggested that MSF has a molecular weight of 70kDa. Schor & Schor (1990) *Cancer Investig.* **8**: 665-667 describes the characterisation of migration stimulating activity (MSF) and gives evidence for its role in cancer pathogenesis. Picardo *et al* (1991) *Lancet* **337**: 130-133 describes the presence of migration stimulating activity in the serum of breast cancer patients. Ellis *et al* (1992) *J. Cell Sci.* **102**: 447-456 describes the antagonistic effects of transforming growth factor-β1 and MSF on fibroblast migration and hyaluronic acid synthesis and discusses the possible implications for wound healing. Picardo *et al* (1992) *Exp. Mol. Path.* **57**: 8-21, describes the identification of migration stimulating factor in wound fluid. Irwin *et al* (1994) *J. Cell Sci.* **107**: 1333-1346, describes the inter- and intra-site heterogeneity in the expression of fetal-like phenotypic characteristics by gingival fibroblasts

and discusses the potential significance for wound healing. Schor *et al* (1994) *Int J Cancer.* 59: 25-32 describes the phenotypic heterogeneity in breast fibroblasts and discusses functional anomaly in fibroblasts from histologically normal tissue adjacent to carcinoma. Schor *et al* (1991) In: *Cell Motility Factors* (ed. I Goldberg) pp. 127-146, Birkhauser Press, Basel, describes the heterogeneity amongst fibroblasts in the production of migration stimulating factor (MSF) and discusses implications for cancer pathogenesis. Schor *et al* (1993) In: *Cell behaviour: Adhesion and Motility*. (ed. G. Evans, C. Wigley and R. Warn) Society for Experimental Biology Symposium No. 47, pp. 234-251, describes the potential structural homology of MSF to the gelatin-binding domain of fibronectin its potential mode of action and possible function in health and disease. A small amount of partial amino acid sequence is given, but this sequence is similar to fibronectin and, in fact, is not present in the MSF which has now been cloned and sequenced in the present work (see below). It is suggested that MSF activity isolated from foetal fibroblast conditioned medium consists of three proteins, one with an apparent molecular weight of 119kDa and a double of 43 and 33kDa, and, indeed, it was suggested that MSF could be a proteotytic degradation product of fibronectin. Schor (1995) In: *Epithelial Mesenchymal Interactions in Cancer* (eg. I Goldberg and E Rosen). pp. 273-296. Birkhauser Press, Basel, describes fibroblast subpopulations as accelerators of tumor progression and the potential role of migration stimulating factor. MSF is also discussed in Schor *et al* (1994) In: Mammary Tumorigenesis and Malignant Progression, Kluwer Academic Publishers, Dickson, R. and Lippman, M. (eds).

Thus, MSF is believed to be produced by fibroblasts obtained from a majority of breast cancer patients and is not made by their normal adult

counterparts. It is believed that measuring the levels of MSF, for example, in circulating blood or in serum or in urine, may be useful in identifying patients who have or are susceptible to cancer, or that it may be useful in prognosing the outcome of cancer. MSF producing fibroblasts are present in patients with a number of common epithelial tumours, such as carcinoma of the breast, lung and colon, as well as melanoma, and soft tissue sarcoma.

It is believed that it may be particularly useful to measure the levels of MSF in identifying patients who have or are susceptible to breast cancer, or in prognosing the outcome of breast cancer.

In addition, it is believed that MSF may be useful in wound healing since it is present in a majority of wound fluid samples. The directed migration of fibroblasts into the wound site and the transient increase in hyaluronic acid in granulation tissue during the wound healing response are both consistent with the involvement of MSF. (MSF stimulates the synthesis of a high molecular weight species of hyaluronic acid).

MSF is known to be related to fibronectin since certain antibodies raised to MSF also bind to fibronectin.

Fibronectin is a widely distributed glycoprotein present at high concentrations in most extracellular matrices, in plasma (300 μg/ml), and in other body fluids. Fibronectin is a prominent adhesive protein and mediates various aspects of cellular interactions with extracellular matrices including migration. Its principal functions appear to be in cellular migration during development and wound healing, regulation of cell growth and differentiation, and haemostasis/thrombosis.

Further progress in understanding MSF was hindered by the fact that it has not been clear whether MSF is a degradation or breakdown product of fibronectin, and because MSF appears to be structurally related to fibronectin.

We have now discovered that MSF is not a breakdown product of fibronectin but that it appears, quite unexpectedly, to be a "mini" splice variant of fibronectin. The amino acid sequence of MSF, disclosed for the first time herein, reveals unexpected regions of dissimilarity with fibronectin. This has led to previously unavailable methods of measuring, identifying and localising MSF becoming available. The availability of a polynucleotide encoding MSF, disclosed for the first time herein, makes available methods for producing MSF and useful variants thereof, and makes available new methods of specifically identifying, measuring and localising MSF.

A first aspect of the invention provides a recombinant polynucleotide encoding a polypeptide comprising the amino acid sequence

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y

Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or variants or fragments or fusions or derivatives thereof, or fusions of said variants or fragments or derivatives.

Figure 2 shows the amino acid sequence encoded by the cDNA insert in pMSF1α which contains the coding sequence for human migration stimulating factor (MSF). Preferably the amino acid sequence is based on that between the most N-terminal methionine and the most C-terminal stop codon (which are marked X). Thus, it is preferred if the polynucleotide encodes a polypeptide comprising the amino acid sequence shown in Figure 2 labelled pMSF1α between positions 19 and 660 (ie. starting MLRGPG... as marked and encoding ...LGY as marked), or variants of fragments or fusions or derivatives thereof or fusions of said variants or fragments.

Throughout the specification where the term MSF is used, and the context does not indicate otherwise, it includes a polypeptide which has an amino acid sequence given in Figure 2 labelled pMSF1α and, in particular, the amino acid sequence given between positions 19 and 660.

Amino acid residues are given in standard single letter code or standard three letter code throughout the specification.

It will be appreciated that the recombinant polynucleotides of the invention are not polynucleotides which encode fibronectin or fragments of fibronectin such as the gelatin binding domain. Preferably, the fragments and variants and derivatives are those that include a polynucleotide which encodes a portion or portions of MSF which are portions that distinguish

MSF from fibronectin and which are described in more detail below and by reference to Figure 2.

The polynucleotide may be DNA or RNA but it is preferred if it is DNA. The polynucleotide may or may not contain introns. It is preferred that it does not contain introns and it is particularly preferred if the polynucleotide is a cDNA.

A polynucleotide of the invention is one which comprises the polynucleotide whose sequence is given in Figure 1. Thus, a polynucleotide of the invention includes the sequence

CAAACTTGGT GGCAACTTGC CTCCCGGTGC GGGCGTCTCT CCCCCACCGT
CTCAACATGC TTAGGGGTCC GGGGCCCGGG CTGCTGCTGC TGGCCGTCCA
GTGCCTGGGG ACAGCGGTGC CCTCCACGGG AGCCTCGAAG AGCAAGAGGC
AGGCTCAGCA AATGGTTCAG CCCCAGTCCC CGGTGGCTGT CAGTCAAAGC
AAGCCCGGTT GTTATGACAA TGGAAAACAC TATCAGATAA ATCAACAGTG
GGAGCGGACC TACCTAGGCA ATGCGTTGGT TTGTACTTGT TATGGAGGAA
GCCGAGGTTT TAACTGCGAG AGTAAACCTG AAGCTGAAGA GACTTGCTTT
GACAAGTACA CTGGGAACAC TTACCGAGTG GGTGACACTT ATGAGCGTCC
TAAAGACTCC ATGATCTGGG ACTGTACCTG CATCGGGGCT GGGCGAGGGA
GAATAAGCTG TACCATCGCA AACCGCTGCC ATGAAGGGGG TCAGTCCTAC
AAGATTGGTG ACACCTGGAG GAGACCACAT GAGACTGGTG GTTACATGTT
AGAGTGTGTG TGTCTTGGTA ATGGAAAAGG AGAATGGACC TGCAAGCCCA
TAGCTGAGAA GTGTTTTGAT CATGCTGCTG GGACTTCCTA TGTGGTCGGA
GAAACGTGGG AGAAGCCCTA CCAAGGCTGG ATGATGGTAG ATTGTACTTG
CCTGGGAGAA GGCAGCGGAC GCATCACTTG CACTTCTAGA AATAGATGCA
ACGATCAGGA CACAAGGACA TCCTATAGAA TTGGAGACAC CTGGAGCAAG
AAGGATAATC GAGGAAACCT GCTCCAGTGC ATCTGCACAG GCAACGGCCG
AGGAGAGTGG AAGTGTGAGA GGCACACCTC TGTGCAGACC ACATCGAGCG
GATCTGGCCC CTTCACCGAT GTTCGTGCAG CTGTTTACCA ACCGCAGCCT
CACCCCCAGC CTCCTCCCTA TGGCCACTGT GTCACAGACA GTGGTGTGGT
CTACTCTGTG GGGATGCAGT GGCTGAAGAC ACAAGGAAAT AAGCAAATGC
TTTGCACGTG CCTGGGCAAC GGAGTCAGCT GCCAAGAGAC AGCTGTAACC
CAGACTTACG GTGGCAACTC AAATGGAGAG CCATGTGTCT TACCATTCAC
CTACAACGAC AGGACGGACA GCACAACTTC GAATTATGAG CAGGACCAGA
AATACTCTTT CTGCACAGAC CACACTGTTT TGGTTCAGAC TCGAGGAGGA
AATTCCAATG GTGCCTTGTG CCACTTCCCC TTCCTATACA ACAACCACAA
TTACACTGAT TGCACTTCTG AGGGCAGAAG AGACAACATG AAGTGGTGTG
GGACCACACA GAACTATGAT GCCGACCAGA AGTTTGGGTT CTGCCCCATG
GCTGCCCACG AGGAAATCTG CACAACCAAT GAAGGGGTCA TGTACCGCAT
TGGAGATCAG TGGGATAAGC AGCATGACAT GGGTCACATG ATGAGGTGCA
CGTGTGTTGG GAATGGTCGT GGGGAATGGA CATGCATTGC CTACTCGCAG
CTTCGAGATC AGTGCATTGT TGATGACATC ACTTACAATG TGAACGACAC

ATTCCACAAG CGTCATGAAG AGGGGCACAT GCTGAACTGT ACATGCTTCG
GTCAGGGTCG GGGCAGGTGG AAGTGTGATC CCGTCGACCA ATGCCAGGAT
TCAGAGACTG GGACGTTTTA TCAAATTGGA GATTCATGGG AGAAGTATGT
GCATGGTGTC AGATACCAGT GCTACTGCTA TGGCCGTGGC ATTGGGGAGT
GGCATTGCCA ACCTTTACAG ACCTATCCAA GCTCAAGTGG TCCTGTCGAA
GTATTTATCA CTGAGACTCC GAGTCAGCCC AACTCCCACC CCATCCAGTG
GAATGCACCA CAGCCATCTC ACATTTCCAA GTACATTCTC AGGTGGAGAC
CTGTGAGTAT CCCACCCAGA AACCTTGGAT ACTGAGTCTC CTAATCTTAT
CAATTCTGAT GGTTTCTTTT TTTCCCAGCT TTTGAGCCAA CAACTCTGAT
TAACTATTCC TATAGCATTT ACTATATTTG TTTAGTGAAC AAACAATATG
TGGTCAATTA AATTGACTTG TAGACTGAAA AAAAAAAAAA AAAAAAA

[SEQ ID NO: 2]

It is particularly preferred if the polynucleotide of the invention is one which comprises the polynucleotide whose sequence is given between positions 57 and 1982 in Figure 1 since this is believed to be the coding sequence for human MSF.

The invention includes a polynucleotide comprising a fragment of the recombinant polynucleotide of the first aspect of the invention. Preferably, the polynucleotide comprises a fragment which is at least 10 nucleotides in length, more preferably at least 14 nucleotides in length and still more preferably at least 18 nucleotides in length. Such polynucleotides are useful as PCR primers.

A "variation" of the polynucleotide includes one which is (i) usable to produce a protein or a fragment thereof which is in turn usable to prepare antibodies which specifically bind to the protein encoded by the said polynucleotide or (ii) an antisense sequence corresponding to the polynucleotide or to a variation of type (i) as just defined. For example, different codons can be substituted which code for the same amino acid(s) as the original codons. Alternatively, the substitute codons may code for a different amino acid that will not affect the activity or immunogenicity of the protein or which may improve or otherwise modulate its activity or immunogenicity. For example, site-directed mutagenesis or other

techniques can be employed to create single or multiple mutations, such as replacements, insertions, deletions, and transpositions, as described in Botstein and Shortle, "Strategies and Applications of *In Vitro* Mutagenesis," *Science*, **229:** 193-210 (1985), which is incorporated herein by reference. Since such modified polynucleotides can be obtained by the application of known techniques to the teachings contained herein, such modified polynucleotides are within the scope of the claimed invention.

Moreover, it will be recognised by those skilled in the art that the polynucleotide sequence (or fragments thereof) of the invention can be used to obtain other polynucleotide sequences that hybridise with it under conditions of high stringency. Such polynucleotides includes any genomic DNA. Accordingly, the polynucleotide of the invention includes polynucleotide that shows at least 55 per cent, preferably 60 per cent, and more preferably at least 70 per cent and most preferably at least 90 per cent homology with the polynucleotide identified in the method of the invention, provided that such homologous polynucleotide encodes a polypeptide which is usable in at least some of the methods described below or is otherwise useful. It is particularly preferred that in this embodiment, the polynucleotide is one which encodes a polypeptide containing a portion or portions that distinguish MSF from fibronectin.

It is believed that MSF is found in mammals other than human. The present invention therefore includes polynucleotides which encode MSF from other mammalian species including rat, mouse, cow, pig, sheep, rabbit and so on.

Per cent homology can be determined by, for example, the GAP program of the University of Wisconsin Genetic Computer Group.

DNA-DNA, DNA-RNA and RNA-RNA hybridisation may be performed in aqueous solution containing between 0.1XSSC and 6XSSC and at temperatures of between 55°C and 70°C. It is well known in the art that the higher the temperature or the lower the SSC concentration the more stringent the hybridisation conditions. By "high stringency" we mean 2XSSC and 65°C. 1XSSC is 0.15M NaCl/0.015M sodium citrate. Polynucleotides which hybridise at high stringency are included within the scope of the claimed invention.

"Variations" of the polynucleotide also include polynucleotide in which relatively short stretches (for example 20 to 50 nucleotides) have a high degree of homology (at least 80% and preferably at least 90 or 95%) with equivalent stretches of the polynucleotide of the invention even though the overall homology between the two polynucleotides may be much less. This is because important active or binding sites may be shared even when the general architecture of the protein is different.

By "variants" of the polypeptide we include insertions, deletions and substitutions, either conservative or non-conservative, where such changes do not substantially alter the activity of the said MSF.

Variants and variations of the polynucleotide and polypeptide include natural variants, including allelic variants and naturally-occurring mutant forms.

MSF may be assessed in bioassays based on its stimulation of adult skin fibroblast migration, for example, as is described in Picardo *et al* (1991) *The Lancet* 337, 130-133. Specificity for MSF may be inferred by neutralisation of migration stimulating activity by anti-MSF polyclonal antibodies (as herein disclosed). MSF may also be assayed using immunological techniques such as ELISA and the like.

By "conservative substitutions" is intended combinations such as Gly, Ala; Val, Ile, Leu; Asp, Glu; Asn, Gln; Ser, Thr; Lys, Arg; and Phe, Tyr.

Such variants may be made using the methods of protein engineering and site-directed mutagenesis well known in the art.

Preferably, the variant or variation of the polynucleotide encodes a MSF that has at least 30%, preferably at least 50% and more preferably at least 70% of the activity of a natural MSF, under the same assay conditions.

By "fragment of MSF" we include any fragment which retains activity or which is useful in some other way, for example, for use in raising antibodies or in a binding assay, but which is not a fragment of MSF which could also be a fragment of fibronectin.

By "fusion of MSF" we include said MSF fused to any other polypeptide. For example, the said protein kinase may be fused to a polypeptide such as glutathione-S-transferase (GST) or protein A in order to facilitate purification of MSF, or it may be fused to some other polypeptide which imparts some desirable characteristics on the MSF fusion. Fusions to any

variant, fragment or derivative of MSF are also included in the scope of the invention.

A further aspect of the invention provides a replicable vector comprising a recombinant polynucleotide encoding MSF, or a variant, fragment, derivative or fusion of MSF or a fusion of said variant, fragment or derivative.

A variety of methods have been developed to operably link polynucleotides, especially DNA, to vectors for example *via* complementary cohesive termini. For instance, complementary homopolymer tracts can be added to the DNA segment to be inserted to the vector DNA. The vector and DNA segment are then joined by hydrogen bonding between the complementary homopolymeric tails to form recombinant DNA molecules.

Synthetic linkers containing one or more restriction sites provide an alternative method of joining the DNA segment to vectors. The DNA segment, generated by endonuclease restriction digestion as described earlier, is treated with bacteriophage T4 DNA polymerase or *E. coli* DNA polymerase I, enzymes that remove protruding, 3'-single-stranded termini with their 3'-5'-exonucleolytic activities, and fill in recessed 3'-ends with their polymerizing activities.

The combination of these activities therefore generates blunt-ended DNA segments. The blunt-ended segments are then incubated with a large molar excess of linker molecules in the presence of an enzyme that is able to catalyze the ligation of blunt-ended DNA molecules, such as bacteriophage T4 DNA ligase. Thus, the products of the reaction are

DNA segments carrying polymeric linker sequences at their ends. These DNA segments are then cleaved with the appropriate restriction enzyme and ligated to an expression vector that has been cleaved with an enzyme that produces termini compatible with those of the DNA segment.

Synthetic linkers containing a variety of restriction endonuclease sites are commercially available from a number of sources including International Biotechnologies Inc, New Haven, CN, USA.

A desirable way to modify the DNA encoding the polypeptide of the invention is to use the polymerase chain reaction as disclosed by Saiki *et al* (1988) *Science* 239, 487-491. This method may be used for introducing the DNA into a suitable vector, for example by engineering in suitable restriction sites, or it may be used to modify the DNA in other useful ways as is known in the art.

In this method the DNA to be enzymatically amplified is flanked by two specific primers which themselves become incorporated into the amplified DNA. The said specific primers may contain restriction endonuclease recognition sites which can be used for cloning into expression vectors using methods known in the art.

The DNA (or in the case of retroviral vectors, RNA) is then expressed in a suitable host to produce a polypeptide comprising the compound of the invention. Thus, the DNA encoding the polypeptide constituting the compound of the invention may be used in accordance with known techniques, appropriately modified in view of the teachings contained herein, to construct an expression vector, which is then used to transform an appropriate host cell for the expression and production of the

polypeptide of the invention. Such techniques include those disclosed in US Patent Nos. 4,440,859 issued 3 April 1984 to Rutter *et al*, 4,530,901 issued 23 July 1985 to Weissman, 4,582,800 issued 15 April 1986 to Crowl, 4,677,063 issued 30 June 1987 to Mark *et al*, 4,678,751 issued 7 July 1987 to Goeddel, 4,704,362 issued 3 November 1987 to Itakura *et al*, 4,710,463 issued 1 December 1987 to Murray, 4,757,006 issued 12 July 1988 to Toole, Jr. *et al*, 4,766,075 issued 23 August 1988 to Goeddel *et al* and 4,810,648 issued 7 March 1989 to Stalker, all of which are incorporated herein by reference.

The DNA (or in the case of retroviral vectors, RNA) encoding the polypeptide constituting the compound of the invention may be joined to a wide variety of other DNA sequences for introduction into an appropriate host. The companion DNA will depend upon the nature of the host, the manner of the introduction of the DNA into the host, and whether episomal maintenance or integration is desired.

Generally, the DNA is inserted into an expression vector, such as a plasmid, in proper orientation and correct reading frame for expression. If necessary, the DNA may be linked to the appropriate transcriptional and translational regulatory control nucleotide sequences recognised by the desired host, although such controls are generally available in the expression vector. The vector is then introduced into the host through standard techniques. Generally, not all of the hosts will be transformed by the vector. Therefore, it will be necessary to select for transformed host cells. One selection technique involves incorporating into the expression vector a DNA sequence, with any necessary control elements, that codes for a selectable trait in the transformed cell, such as antibiotic resistance.

Alternatively, the gene for such selectable trait can be on another vector, which is used to co-transform the desired host cell.

Host cells that have been transformed by the recombinant DNA of the invention are then cultured for a sufficient time and under appropriate conditions known to those skilled in the art in view of the teachings disclosed herein to permit the expression of the polypeptide, which can then be recovered.

Many expression systems are known, including bacteria (for example *E. coli* and *Bacillus subtilis*), yeasts (for example *Saccharomyces cerevisiae*), filamentous fungi (for example *Aspergillus*), plant cells, animal cells and insect cells.

The vectors typically include a prokaryotic replicon, such as the ColE1 *ori*, for propagation in a prokaryote, even if the vector is to be used for expression in other, non-prokaryotic, cell types. The vectors can also include an appropriate promoter such as a prokaryotic promoter capable of directing the expression (transcription and translation) of the genes in a bacterial host cell, such as *E. coli*, transformed therewith.

A promoter is an expression control element formed by a DNA sequence that permits binding of RNA polymerase and transcription to occur. Promoter sequences compatible with exemplary bacterial hosts are typically provided in plasmid vectors containing convenient restriction sites for insertion of a DNA segment of the present invention.

Typical prokaryotic vector plasmids are pUC18, pUC19, pBR322 and pBR329 available from Biorad Laboratories, (Richmond, CA, USA) and p*Trc*99A and pKK223-3 available from Pharmacia, Piscataway, NJ, USA.

A typical mammalian cell vector plasmid is pSVL available from Pharmacia, Piscataway, NJ, USA. This vector uses the SV40 late promoter to drive expression of cloned genes, the highest level of expression being found in T antigen-producing cells, such as COS-1 cells.

An example of an inducible mammalian expression vector is pMSG, also available from Pharmacia. This vector uses the glucocorticoid-inducible promoter of the mouse mammary tumour virus long terminal repeat to drive expression of the cloned gene.

Useful yeast plasmid vectors are pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (YIps) and incorporate the yeast selectable markers *HIS3*, *TRP1*, *LEU2* and *URA3*. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps).

Other vectors and expression systems are well known in the art for use with a variety of host cells.

The present invention also relates to a host cell transformed with a polynucleotide vector construct of the present invention. The host cell can be either prokaryotic or eukaryotic. Bacterial cells are preferred prokaryotic host cells and typically are a strain of *E. coli* such as, for example, the *E. coli* strains DH5 available from Bethesda Research

Laboratories Inc., Bethesda, MD, USA, and RR1 available from the American Type Culture Collection (ATCC) of Rockville, MD, USA (No ATCC 31343). Preferred eukaryotic host cells include yeast, insect and mammalian cells, preferably vertebrate cells such as those from a mouse, rat, monkey or human fibroblastic and kidney cell lines. Yeast host cells include YPH499, YPH500 and YPH501 which are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Preferred mammalian host cells include Chinese hamster ovary (CHO) cells available from the ATCC as CCL61, NIH Swiss mouse embryo cells NIH/3T3 available from the ATCC as CRL 1658, monkey kidney-derived COS-1 cells available from the ATCC as CRL 1650 and 293 cells which are human embryonic kidney cells. Preferred insect cells are Sf9 cells which can be transfected with baculovirus expression vectors.

Transformation of appropriate cell hosts with a DNA construct of the present invention is accomplished by well known methods that typically depend on the type of vector used. With regard to transformation of prokaryotic host cells, see, for example, Cohen *et al* (1972) *Proc. Natl. Acad. Sci. USA* **69**, 2110 and Sambrook *et al* (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY. Transformation of yeast cells is described in Sherman *et al* (1986) *Methods In Yeast Genetics, A Laboratory Manual*, Cold Spring Harbor, NY. The method of Beggs (1978) *Nature* **275**, 104-109 is also useful. With regard to vertebrate cells, reagents useful in transfecting such cells, for example calcium phosphate and DEAE-dextran or liposome formulations, are available from Stratagene Cloning Systems, or Life Technologies Inc., Gaithersburg, MD 20877, USA.

Electroporation is also useful for transforming and/or transfecting cells and is well known in the art for transforming yeast cell, bacterial cells, insect cells and vertebrate cells.

For example, many bacterial species may be transformed by the methods described in Luchansky *et al* (1988) *Mol. Microbiol.* 2, 637-646 incorporated herein by reference. The greatest number of transformants is consistently recovered following electroporation of the DNA-cell mixture suspended in 2.5X PEB using 6250V per cm at 25μFD.

Methods for transformation of yeast by electroporation are disclosed in Becker & Guarente (1990) *Methods Enzymol.* **194**, 182.

Successfully transformed cells, ie cells that contain a DNA construct of the present invention, can be identified by well known techniques. For example, cells resulting from the introduction of an expression construct of the present invention can be grown to produce the polypeptide of the invention. Cells can be harvested and lysed and their DNA content examined for the presence of the DNA using a method such as that described by Southern (1975) *J. Mol. Biol.* 98, 503 or Berent *et al* (1985) *Biotech.* 3, 208. Alternatively, the presence of the protein in the supernatant can be detected using antibodies as described below.

In addition to directly assaying for the presence of recombinant DNA, successful transformation can be confirmed by well known immunological methods when the recombinant DNA is capable of directing the expression of the protein. For example, cells successfully transformed with an expression vector produce proteins displaying appropriate antigenicity.

Samples of cells suspected of being transformed are harvested and assayed for the protein using suitable antibodies.

Thus, in addition to the transformed host cells themselves, the present invention also contemplates a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived from a monoclonal culture, in a nutrient medium.

A further aspect of the invention provides a method of making MSF or a variant, derivative, fragment or fusion thereof or a fusion of a variant, fragment or derivative, the method comprising culturing a host cell comprising a recombinant polynucleotide or a replicable vector which encodes said MSF or variant or fragment or derivative or fusion, and isolating said MSF or a variant, derivative, fragment or fusion thereof of a fusion or a variant, fragment or derivative from said host cell.

Methods of cultivating host cells and isolating recombinant proteins are well known in the art. It will be appreciated that, depending on the host cell, the MSF produced may differ from that which can be isolated from nature. For example, certain host cells, such as yeast or bacterial cells, either do not have, or have different, post-translational modification systems which may result in the production of forms of MSF which may be post-translationally modified in a different why to MSF isolated from nature. It is preferred if the host cell is a non-human host cell; move preferably it is not a mammalian cell.

It is preferred that recombinant MSF is produced in a eukaryotic system, such as an insect cell.

A further aspect of the invention provides MSF or a variant, fragment, derivative or fusion thereof or a fusion of a variant, fragment or derivative obtainable by the methods herein disclosed.

A further aspect of the invention provides a polypeptide comprising the amino acid sequence

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N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y
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[SEQ ID NO: 1]

or variants or fragments or fusions or derivatives thereof or fusions of said variants or fragments or derivatives.

Thus, a polypeptide of the invention includes

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N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
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M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

Preferably, the polypeptide comprises the amino acid sequence shown in Figure 2 labelled pMSF1α between positions 19 and 660, or variants or fragments or fusions or derivatives thereof or fusions of said variants or fragments or derivatives.

It will be appreciated that the polypeptides of the invention are not fibronectin or fragments of fibronectin such as the gelatin binding domain. Preferably, the fragments and variants and derivatives are those that include a portion or portions of MSF which are portions that distinguish MSF from fibronectin and which are described in more detail below and by reference to Figure 2.

Preferably, the polypeptide of the invention is one which has migration stimulating factor activity.

Further aspects of the invention provide antibodies which are selective for MSF (and do not cross react with fibronectin) and antibodies which are selective for fibronectin (and do not cross react with MSF).

By "selective" we include antibodies which bind at least 10-fold more strongly to one polypeptide than to the other (ie MSF *vs* fibronectin); preferably at least 50-fold more strongly and more preferably at least 100-fold more strongly.

Such antibodies may be made by methods well known in the art using the information concerning the differences in amino acid sequence between MSF and fibronectin disclosed herein. In particular, the antibodies may be polyclonal or monoclonal.

Suitable monoclonal antibodies which are reactive as said may be prepared by known techniques, for example those disclosed in "*Monoclonal Antibodies: A manual of techniques*", H Zola (CRC Press, 1988) and in "Monoclonal Hybridoma Antibodies: Techniques and Applications", SGR Hurrell (CRC Press, 1982). Polyclonal antibodies may be produced which are polyspecific or monospecific. It is preferred that they are monospecific.

One embodiment provides an antibody reactive towards the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or natural variants thereof but not reactive towards fibronectin.

A further embodiment provides an antibody reactive towards the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α between positions 19 and 660 or natural variants thereof but not reactive towards fibronectin.

A further embodiment provides an antibody reactive towards an epitope present in the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α or natural variants thereof but which epitope is not present in fibronectin.

A further embodiment provides an antibody reactive towards an epitope present in the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

between positions 19 and 660 or natural variants thereof but which is epitope is not present in fibronectin.

It is particularly preferred if the antibody is reactive towards a molecule comprising any one of the peptides:

ISKYILRWRPVSIPPRNLGY; [SEQ ID NO: 3]; or

QQWERTYLGNALVCTCYGGSR; [SEQ ID NO: 4]; or

PCVLPFTYNDRTDSTTSNYEQDQ; [SEQ ID NO: 5]; or

TDHTVLVQTRGGNSNGALCH; [SEQ ID NO: 6]; or

VGNGRGEWTCIAYSQLRDQCI [SEQ ID NO: 7]

which are found in MSF. The underlined amino acid(s) indicate the difference between MSF and fibronectin.

These peptides contain and flank regions of difference in amino acid sequence between MSF and fibronectin as shown in Figure 2 which are believed to be useful in distinguishing MSF and fibronectin using antibodies.

A further embodiment provides an antibody reactive towards fibronectin but not reactive towards the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1 or natural variants thereof.

A further embodiment provides an antibody reactive towards fibronectin but not reactive towards the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1 between positions 19 and 660 or natural variants thereof.

A further embodiment provides an antibody reactive towards an epitope present in fibronectin but not present in the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or natural variants thereof.

A further embodiment provides an antibody reactive towards an epitope present in fibronectin but not present in the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α between positions 19 and 660 or natural variants thereof.

It is particularly preferred if the antibody is reactive towards a molecule comprising any one of the peptides:

QQWERTYLGNVLVCTCYGGSR [SEQ ID NO: 8] or
EPCVLPFTYNGRTFYSCTTEGRQDGHLWCSTTSNYEQDQ [SEQ ID NO: 9] or
CTDHTVLVQTQGGNSNGALCH [SEQ ID NO: 10] or
VGNGRGEWTCYAYSQLRDQCI [SEQ ID NO: 11] or
ISKYILRWRPKNSVGRWKEA [SEQ ID NO: 12] or

peptides derived from position 648 onwards in fibronectin as shown in Figure 2. The underlined amino acid(s) indicate the difference between fibronectin and MSF.

These peptides themselves may be useful for raising antibodies, but selective antibodies may be made using smaller fragments of these peptides which contain the region of difference between MSF and fibronectin.

Peptides in which one or more of the amino acid residues are chemically modified, before or after the peptide is synthesised, may be used providing that the function of the peptide, namely the production of specific antibodies *in vivo*, remains substantially unchanged. Such modifications include forming salts with acids or bases, especially physiologically acceptable organic or inorganic acids and bases, forming an ester or amide of a terminal carboxyl group, and attaching amino acid protecting groups such as N-t-butoxycarbonyl. Such modifications may protect the peptide from *in vivo* metabolism. The peptides may be present as single copies or as multiples, for example tandem repeats. Such tandem or multiple repeats may be sufficiently antigenic themselves to obviate the use of a carrier. It may be advantageous for the peptide to be formed as a loop, with the N-terminal and C-terminal ends joined together, or to add one or more Cys residues to an end to increase antigenicity and/or to allow disulphide bonds to be formed. If the peptide is covalently linked to a carrier, preferably a polypeptide, then the arrangement is preferably such that the peptide of the invention forms a loop.

According to current immunological theories, a carrier function should be present in any immunogenic formulation in order to stimulate, or enhance stimulation of, the immune system. It is thought that the best carriers embody (or, together with the antigen, create) a T-cell epitope. The

peptides may be associated, for example by cross-linking, with a separate carrier, such as serum albumins, myoglobins, bacterial toxoids and keyhole limpet haemocyanin. More recently developed carriers which induce T-cell help in the immune response include the hepatitis-B core antigen (also called the nucleocapsid protein), presumed T-cell epitopes such as Thr-Ala-Ser-Gly-Val-Ala-Glu-Thr-Thr-Asn-Cys [SEQ ID NO: 13], beta-galactosidase and the 163-171 peptide of interleukin-1. The latter compound may variously be regarded as a carrier or as an adjuvant or as both. Alternatively, several copies of the same or different peptides of the invention may be cross-linked to one another; in this situation there is no separate carrier as such, but a carrier function may be provided by such cross-linking. Suitable cross-linking agents include those listed as such in the Sigma and Pierce catalogues, for example glutaraldehyde, carbodiimide and succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate, the latter agent exploiting the -SH group on the C-terminal cysteine residue (if present).

If the peptide is prepared by expression of a suitable nucleotide sequence in a suitable host, then it may be advantageous to express the peptide as a fusion product with a peptide sequence which acts as a carrier. Kabigen's "Ecosec" system is an example of such an arrangement.

The peptide of the invention may be linked to other antigens to provide a dual effect.

A further aspect of the invention provides a method of making an antibody which is reactive towards the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K

R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof and which is not reactive with fibronectin, the method comprising the steps of, where appropriate, immunising an animal with a peptide which distinguishes MSF from fibronectin and selecting an antibody which binds MSF but does not substantially bind fibronectin. Suitable peptides are disclosed above.

A still further aspect of the invention provides a method of making an antibody which is reactive towards fibronectin and which is not reactive towards the polypeptide whose amino acid sequence is [SEQ ID NO: 1]

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C

D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or a natural variant thereof, the method comprising the steps of, where appropriate, immunising an animal with a peptide which distinguishes fibronectin from MSF and selecting an antibody which binds fibronectin but does not substantially bind MSF. Suitable peptides are disclosed above.

It will be appreciated that, with the advancements in antibody technology, it may not be necessary to immunise an animal in order to produce an antibody. Synthetic systems, such as phage display libraries, may be used. The use of such systems is included in the methods of the invention.

Before the present invention it was not possible to make use of the differences in amino acid sequence between fibronectin and MSF in order to make antibodies which are useful in distinguishing MSF and fibronectin since it was not known that MSF and fibronectin had significant differences in structure or what those differences were. As is discussed in more detail below, such antibodies are useful in cancer diagnosis. It will also be appreciated that such antibodies which distinguish MSF and fibronectin are also useful research reagents. Suitably, the antibodies of the invention are detectably labelled, for example they may be labelled in such a way that they may be directly or indirectly detected. Conveniently, the antibodies are labelled with a radioactive moiety or a coloured moiety or a fluorescent moiety, or they may be linked to an enzyme. Typically, the enzyme is one which can convert a non-coloured (or non-fluorescent) substrate to a coloured (or fluorescent) product. The antibody may be labelled by biotin (or streptavidin) and then detected indirectly using

streptavidin (or biotin) which has been labelled with a radioactive moiety or a coloured moiety or a fluorescent moiety, or the like or they may be linked to an enzyme of the type described above.

It is particularly preferred if peptides are made, based on the amino acid sequence of MSF and fibronectin, which allow for specific antibodies to be made.

Thus, a further aspect of the invention provides a molecule which is capable of, following immunisation of an animal if appropriate, giving rise to antibodies which are reactive towards the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or natural variants thereof but not reactive towards fibronectin.

A still further aspect of the invention provides a molecule which is capable of, following immunisation of an animal if appropriate, giving rise to

antibodies which are reactive towards fibronectin but not reactive towards the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or natural variants thereof.

The molecule is preferably a peptide but may be any molecule which gives rise to the desired antibodies. The molecule, preferably a peptide, is conveniently formulated into an immunological composition using methods well known in the art.

The peptides disclosed above form part of these aspects of the invention.

Peptides may be synthesised by the Fmoc-polyamide mode of solid-phase peptide synthesis as disclosed by Lu *et al* (1981) *J. Org. Chem.* **46**, 3433 and references therein. Temporary N-amino group protection is afforded by the 9-fluorenylmethyloxycarbonyl (Fmoc) group. Repetitive cleavage of this highly base-labile protecting group is effected using 20% piperidine in N,N-dimethylformamide. Side-chain functionalities may be protected as their butyl ethers (in the case of serine threonine and tyrosine), butyl

esters (in the case of glutamic acid and aspartic acid), butyloxycarbonyl derivative (in the case of lysine and histidine), trityl derivative (in the case of cysteine) and 4-methoxy-2,3,6-trimethylbenzenesulphonyl derivative (in the case of arginine). Where glutamine or asparagine are C-terminal residues, use is made of the 4,4'-dimethoxybenzhydryl group for protection of the side chain amido functionalities. The solid-phase support is based on a polydimethyl-acrylamide polymer constituted from the three monomers dimethylacrylamide (backbone-monomer), bisacryloylethylene diamine (cross linker) and acryloylsarcosine methyl ester (functionalising agent). The peptide-to-resin cleavable linked agent used is the acid-labile 4-hydroxymethyl-phenoxyacetic acid derivative. All amino acid derivatives are added as their preformed symmetrical anhydride derivatives with the exception of asparagine and glutamine, which are added using a reversed N,N-dicyclohexyl-carbodiimide/1-hydroxybenzotriazole mediated coupling procedure. All coupling and deprotection reactions are monitored using ninhydrin, trinitrobenzene sulphonic acid or isotin test procedures. Upon completion of synthesis, peptides are cleaved from the resin support with concomitant removal of side-chain protecting groups by treatment with 95% trifluoroacetic acid containing a 50% scavenger mix. Scavengers commonly used are ethanedithiol, phenol, anisole and water, the exact choice depending on the constituent amino acids of the peptide being synthesised. Trifluoroacetic acid is removed by evaporation *in vacuo*, with subsequent trituration with diethyl ether affording the crude peptide. Any scavengers present are removed by a simple extraction procedure which on lyophilisation of the aqueous phase affords the crude peptide free of scavengers. Reagents for peptide synthesis are generally available from Calbiochem-Novabiochem (UK) Ltd, Nottingham NG7 2QJ, UK. Purification may be effected by any one, or a combination of, techniques

such as size exclusion chromatography, ion-exchange chromatography and (principally) reverse-phase high performance liquid chromatography. Analysis of peptides may be carried out using thin layer chromatography, reverse-phase high performance liquid chromatography, amino-acid analysis after acid hydrolysis and by fast atom bombardment (FAB) mass spectrometric analysis.

It is now possible to make polynucleotides which can distinguish MSF and fibronectin and such polynucleotides are believed to be useful in the diagnosis and prognosis of cancer.

A further aspect of the invention provides a polynucleotide which is capable of distinguishing a polynucleotide which encodes the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof and a polynucleotide which encodes fibronectin.

A still further aspect of the invention provides a polynucleotide which is capable of hybridising to a polynucleotide which encodes fibronectin but not a polynucleotide which encodes the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof.

A yet still further aspect of the invention provides a polynucleotide which is capable of hybridising to a polynucleotide which encodes the polypeptide which encodes the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T

S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof but not to a polynucleotide which encodes fibronectin.

Such polynucleotides can be designed by reference to Figures 1 and 2 and the known sequence of fibronectin (Kornblihtt *et al* (1985) *EMBO J.* 4, 1755-1759), and may be synthesised by well known methods such as by chemical synthesis or by using specific primers and template, a DNA amplification technique such as the polymerase chain reaction. The polynucleotide may be any polnucleotide, whether DNA or RNA or a synthetic nucleic acid such as a peptide nucleic acid, provided that it can distinguish polynucleotides which encode MSF and fibronectin as said. It is particularly preferred if the polynucleotide is an oligonucleotide which can serve as a hybridisation probe or as a primer for a nucleic acid amplification system. Thus, the polynucleotide of this aspect of the invention may be an oligonucleotide of at least 10 nucleotides in length, more preferably at least 14 nucleotides in length and still more preferably at least 18 nucleotides in length.

It is particularly preferred that the polynucleotide hybridises to a mRNA (or cDNA) which encodes MSF but does not hybridise to a mRNA (or cDNA) which encodes fibronectin.

It is also particularly preferred that the polynucleotide hybridises to a mRNA (or cDNA) which encodes fibronectin but does not hybridise to a

mRNA (or cDNA) which encodes MSF. The nucleotide sequence of MSF cDNA is disclosed herein and the nucleotide sequence of fibronectin is known (for example, see Kornblihtt *et al* (1985) *EMBO J.* 4, 1755-1759). The skilled person can readily design probes which can distinguish MSF and fibronectin mRNAs and cDNAs based on this information. Differences between MSF and fibronectin include a 45 bp deletion from the first type II fibronectin repeat module in MSF, and the unique tail present in MSF.

Preferably, the polynucleotides of the invention are detectably labelled. For example, they may be labelled in such a way that they may be directly or indirectly detected. Conveniently, the polynucleotides are labelled with a radioactive moiety or a coloured moiety or a fluorescent moiety or some other suitable detectable moiety. The polynucleotides may be linked to an enzyme, or they may be linked to biotin (or streptaridin) and detected in a similar way as described for antibodies of the invention.

A further aspect of the invention provides a method of diagnosing cancer the method comprising detecting in a sample from the person to be diagnosed the presence of a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y

N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant or fragment thereof using a reagent which can distinguish said polypeptide from fibronectin.

A still further aspect of the invention provides a method of determining susceptibility to cancer the method comprising detecting in a sample derived from the person to be tested the presence of a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant or fragment thereof using a reagent which can distinguish said polypeptide from fibronectin.

A still further aspect of the invention provides a method of determining the likely outcome of a patient with cancer the method comprising

detecting in a sample from the patient the presence of a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant or fragment thereof using a reagent which can distinguish said polypeptide from fibronectin.

Preferably, the reagent which can distinguish MSF from fibronectin is an antibody as disclosed herein. The use of antibodies to detect specific polypeptides in samples is well known. For example, they can be used in enzyme-linked immunosorbend assays (ELISA) or they may be used in histopathological analysis. It is believed that the presence of MSF indicates an elevated risk of cancer.

MSF may be conveniently measured in suitable body fluids such as serum or urine, or in extracts of tissue, or in the medium used to culture patient derived cells *in vitro*.

The measurement of MSF is believed to be useful in a number of cancers as discussed above. Antibodies may be used to detect MSF in tissue sections by immunolocalisation. Sub-populations of MSF-producing fibroblasts are present in the normal adult (Irwin *et al* (1994) *J. Cell Science* **107**, 1333-1346; Schor *et al* (1994) pp 277-298 in Mammary Tumorigenesis and Malignant Progression, Dickson, R. and Lippman, M. (eds), 1994, Kluwer Academic Publishers.

It will be appreciated that, as well as the MSF polypeptide being measured using the methods described herein in diagnosis or prognosis or determination of susceptibility to cancer, it may be desirable to detect MSF mRNA in a suitable sample or it may be desirable to detect any changes in the fibronectin gene which are associated with the production of MSF. Mutations in the MSF cDNA or fibronectin gene may be detected using methods well known in the art.

Thus, a further aspect of the invention provides a method of determining susceptibility to cancer the method comprising detecting in a sample derived from the person to be tested the presence of a polynucleotide encoding a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y

N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant or fragment thereof using a reagent which can distinguish said polynucleotide from a polynucleotide encoding fibronectin.

A still further aspect of the invention provides a method of determining the likely outcome of a patient with cancer the method comprising detecting in a sample from the patient the presence of a polynucleotide encoding a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant or fragment thereof using a reagent which can distinguish said polynucleotide from a polynucleotide encoding fibronectin.

Preferably, the reagent which can distinguish the polynucleotide encoding MSF from the polynucleotide encoding fibronectin is a suitable polynucleotide as disclosed herein. Methods of detecting specific nucleic acids in a sample are well known in the art. For example, *in situ* hybridisation methods which detect mRNA may be used, and northern blotting methods may be used. Dot blots, slot blots and Southern blots may also be used.

Thus, it can be seen that the reagents used in the above methods may be used in the manufacture of a reagent for diagnosing cancer.

It will be appreciated that the antibodies of the invention, and the polynucleotides of the invention, which can distinguish MSF and fibronectin (particularly those which recognise MSF or a nucleic acid encoding MSF, but not fibronectin, or a nucleic acid encoding fibronectin) are useful packaged into diagnostic kits containing said antibodies or polynucleotides and other reagents such as means for labelling the said antibodies or polynucleotides.

The invention also includes a number of therapeutic applications, for example chemoprevention and chemotherapy.

Chemoprevention includes the neutralisation of MSF activity and/or the suppression of inappropriate MSF expression in individuals deemed to be at risk of cancer due to inappropriate MSF production. It may also be desirable to administer inhibitors of MSF. Antibodies directed at MSF may act as inhibitors.

Chemotherapy includes the use of anti-MSF antibodies to target coupled cytotoxins to sites of inappropriate MSF production, and the use of MSF inhibitors as mentioned above.

Antibody-targeted cytotoxins are well known in the art and include antibodies linked to a directly cytotoxic moiety such as ricin or a toxic drug; and antibodies linked to an indirectly cytotoxic moiety such as an enzyme which is able to convert a non-toxic prodrug into a toxic drug. In the latter case, the prodrug as well as the antibody-linked enzyme is administered to the patient.

It is useful to measure MSF in wound fluids since this information may be relevant in terms of predicting the efficiency of the subsequent healing process, including the propensity of the scar. The amount of MSF in wound fluids may be measured using, for example, an MSF-selective antibody of the invention.

Inappropriate expression of MSF may be a feature of several pathological conditions characterised by inflammation, such as rheumatoid arthritis. The measurement of MSF in associated body fluid, such as synovial fluid, may be of clinical utility; other pathological conditions of relevance in this context include fibrotic and periodontal disease.

MSF is believed to be involved in the migration of cells, especially fibroblasts any, in particular, the migration of cells may take place within the wound.

Thus, a further aspect of the invention provides a method of modulating cell migration the method comprising administering an effective amount of

a polypeptide of the invention to the site where modulation of cell migration is required.

Typically, the cell whose migration is modulated is a fibroblast. Typically, MSF stimulates the migration of cells such as fibroblasts. Preferably, the site where modulation of cell migration is required is a site within a mammalian body, such as the body of a horse, pig, cow, sheep, cat, dog and the like. Most preferably it is a site within a human body. It is preferred if the site within the body is the site of a wound.

A further aspect of the invention provides a method of healing a wound the method comprising administering to the locality of the wound an effective amount of a polypeptide of the invention.

The invention also includes a method of preventing scarring by administering to the locality of the site where scarring is believed to be likely an effective amount of an MSF polypeptide as described herein or a suitable fragment or variant. Preventing or reducing scarring may be part of the wound-healing process. The MSF polypeptide as described herein or a suitable fragment or variant is believed to be useful in preventing or reducing scarring because it reduces hyaluronic acid formation.

It is preferred if the polypeptide administered is a recombinant polypeptide expressed in a eukaryotic host.

The MSF polypeptide may be administered to the site of cell migration or wound healing by any suitable means. Conveniently, the polypeptide is administered topically. It is particularly preferred if the polypeptide is incorporated within an applied wound dressing such as a collagen mesh.

Dressings which are suitable for the incorporation of the polypeptide of the invention are well known in the art and many are commercially available.

Other formulations might involve the incorporation of MSF into an ointment, paste, gel, cream (or equivalent) designed for topical application.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (polypeptide of the invention) with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations in accordance with the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient

in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouth-washes comprising the active ingredient in a suitable liquid carrier.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

Application of gene therapy techniques may provide a means of controlling MSF expression.

Any suitable amount of the polypeptide of the invention may be administered. By "suitable amount" we mean an amount which gives the desired biological response and that does not lead to any significantly undesirable effects such as toxicity or the like. Small quantities of MSF, for example less than 1 μg, may be effective. It is preferred if superficial wounds, such as those to the skin, are treated by the method of the invention.

The invention will now be described in further detail with reference to the following Figures and Examples wherein:

Figure 1 shows the entire nucleotide sequence of the 2.1kb insert in clone pMSF1α which contains the MSF cDNA. The start and stop codons are underlined.

Figure 2 shows the translation of the cDNA sequence shown in Figure 1 and the alignment of the peptide sequence with that of the gelatin-binding

domain of fibronectin. The start and end of the MSF polypeptide are indicated by vertical bars and arrows.

Figure 3 shows the peptide sequence of MSF (as encoded in the pMSF1α clone) according to its domains. The sequence of pMSF1α is shown grouped according to its domains (cf analysis of fibronectin from Kornblihtt *et al* (1985) *EMBO J.* **4**, 1755-1759). Residues are numbered and have been aligned to give optimal homology by introducing gaps (indicated by ^). Identical residues within a type of homology are indicated by a box (A), and stop codons are designated by asterisks (*). Deleted amino acids are indicated by dashed lines (-), and the IGDS sequence is underlined.

Figure 4 shows a diagrammatic comparison of fibronectin and MSF.

Figure 5 shows a diagrammatic model of MSF showing the positions of the IGD-containing sequences (ie. IGDT, IGDS and IGDQ) within the domains.

Example 1: Cloning and sequence analysis of pMSF1α, a clone encoding MSF

A cDNA library was constructed using mRNA extracted from a human foetal fibroblast cell line, MRC5-SV2, in the vector λZapII.

A primer based on peptide sequence from the gelatin-binding domain (GBD) of fibronectin was used together with a vector primer in the polymerase chain reaction (PCR) to amplify a fragment of 1.2kb. Sequence analysis showed a strong homology to GBD for most of the

fragment. Clear differences included an internal deletion of 45bp, and a 3' unique sequence of 175bp.

The 3' unique sequence was used as a probe for screening the library, using the digoxigenin-labelled system. Positive plaques were picked for further analysis by secondary and tertiary screening, followed by *in vivo* excision of the pBluescript™ phagemid containing the cloned insert.

A plasmid containing an insert of 2.1kb, named pMSF1α, was sequenced by the Sanger-dideoxy method, using a progressive priming approach, and the sequence was assembled into a single contain using the Fragment Assembly System of the Daresbury/Seqnet series of programs.

The entire nucleotide sequence of the 2.1kb fragment is shown in Figure 1.

Translation of this sequence and alignment of its peptide sequence with that of the gelatin-binding domain of fibronectin was achieved using the Fasta program (Daresbury/Seqnet), and is shown in Figure 2.

Figure 3 shows the peptide sequence of pMSF-1α grouped according to its domains.

Other cDNA clones encoding MSF may be readily obtained and sequenced using methods well known in the art and probe derived from the Figure 1 sequence, in particular probes which distinguish MSF from fibronectin.

Example 2: Demonstration of the presence of MSF-secreting fibroblasts in sections of breast cancer, but not normal breast tissue

In situ hybridisation using a riboprobe based on the unique coding region for the unique C-terminus of MSF demonstrates the presence of MSF-secreting fibroblasts in sections of breast cancer, but not normal breast tissue.

Suitable riboprobes contain the entire unique nucleotide sequence of MSF-1α (position 1953-2147), and may include up to 10 bases upstream and contained within the fibronectin sequence (position 1943-2152). This ensures high specificity towards MSF-1α, whilst allowing the use of a probe of longer length. A digoxigenin-labelled riboprobe containing a major portion of the unique sequence (position 1974-2147) is used. This region was selected on the basis of the position of convenient restriction sites.

Example 3: Monoclonal antibodies which are specific to MSF and do not cross-react with fibronectin

Monoclonal antibodies are raised using any of the currently available standard procedures. The immunogen is a synthetic peptide based on the 10 amino acid unique tail of MSF or is based on the peptide sequences:

ISKYILRWRPVSIPPRNLGY; [SEQ ID NO: 3]; or
QQWERTYLGNALVCTCYGGSR; [SEQ ID NO: 4]; or
PCVLPFTYNDRTDSTTSNYEQDQ; [SEQ ID NO: 5]; or
TDHTVLVQTRGGNSNGALCH; or [SEQ ID NO: 6]; or
VGNGRGEWTCIAYSQLRDQCI [SEQ ID NO: 7]

Example 4: Genomic PCR and FISH studies

Objective: To obtain information regarding the sequence of the genomic MSF gene regarding (i) its relationship to fibronectin, and (ii) chromosomal location.

Background: The 5′ upstream untranslated sequence of the cloned MSF cDNA is identical to that of fibronectin, thereby strongly suggesting its close relationship to the fibronectin gene (note: such upstream untranslated regions are virtually never identical between two genes as there is no selective pressure. This inference is in apparent conflict with the "uniqueness" of the 3′ end of the MSF cDNA which codes for a 10 amino acid polypeptide and also contains a contiguous untranslated region containing several stop codons).

Methods and Results: Two PCR reactions were established: one at the extreme 5′ untranslated region of fibronectin (FN)/MSF and the other at the extreme 3′ region of MSF which encompassed the 175bp unique sequence. Reactions were carried out using DNA purified using the *Qiagen* Blood kit. Sequence analysis of the resulting amplicon revealed that the 175bp "unique" sequence was contiguous with the fibronectin sequence.

Experiments were then carried out in order to obtain initial data regarding the genomic location of the 3′ unique sequence. This was accomplished by selecting clones from the human PAC library (obtained from HGMP) using the above 2 PCR approach. Secondary and tertiary screening lead

to the identification of on which produced products from *both* PCR reactions. This clone was approximately 70-110 kb in size.

The isolated clone was next subjected to restriction digestion (BamHI and KpnI) and the fragments subcloned into pBluescript and analysed using our 2 PCR approach. Two positive clones were identified: clone B3(2) is 20 kb and can generate both the 5′ and 3′ fragments, thereby indicating that it contains the entire MSF genomic sequence. The other clone, K5(5) is 7 kb and only contains the 3′ unique sequence.

We have used both clones for FISH analysis of the human genome. Our data unambiguously indicate that MSF maps to chromosome 2 region q35. Note: this is within the fibronectin gene, which is located on chromosome 2q34-36.

Conclusions: The FISH analysis clearly indicates that the gene coding for the MSF "unique" sequence is contained within the fibronectin gene. These results indicate that MSF is a novel "mini" splice variant of fibronectin. The genomic fibronectin gene is very large indeed and has still not been fully sequenced. To our knowledge, this is the first report of the unique sequence. The absence of the unique sequence in all previously identified isoforms of fibronectin (which are all in excess of 220 kDa compared to 70 kDa for MSF) indicates that it is spliced out of these molecules.

This information is of relevance for several reasons. Firstly, all previously described splice variants of fibronectin have molecular masses in the region of 225 kDa compared with only 70 kDa of MSF. This small size is totally unexpected and prompts us to refer to MSF as a novel

"mini" splice variant of fibronectin. Secondly, all known splice variants of fibronectin involve the inclusion/deletion of entire type III repeats or variable regions of the IIICS region (all of which occur at a considerable distance downstream of the termination of MSF, which does not contain any known splice site). Finally, as the unique 3'-sequence of MSF was not hitherto identified, it was not possible to predict that MSF was indeed a splice variant of fibronectin until the above data was obtained from genomic DNA.

Example 5: Recombinant MSF expression

Objective: To express recombinant human MSF (rhMSF) in 3T3 cells.

Methods and Results: 3T3 cells were transfected using the Lipfectamine/Plus system (Gibco), according to the manufacturer's instructions. The plasmid used was pcDNA3.1/hisB/lacZ. The insert sequence contained a sequence encoding a *his* tail fused to the human MSF cDNA sequence so that a fusion protein with a *his* tail is expressed. This facilitates purification of the expressed protein. Transfectants were isolated by their selective growth in medium containing 418. One liter of conditioned medium produced by the transfected cells was collected and the fraction containing all the migration stimulating activity obtained by doing a 0-20% ammonium sulphate precipitation. The pellet was resuspended in buffer and the *his*-tagged rhMSF purified by passage through a ProBond column (Invitrogen) column, all done in accordance with manufacturer's instructions. Approximately 250 µg of rhMSF were collected from the starting material. The purified protein resulted in a single band of approximately 70 kDa in SDS PAGE. This protein stimulated the migration of target adult fibroblasts and was active at

concentrations between 1 pg/ml to 10 ng/ml (ie in precise agreement with previously published data regarding the dose-response of MSF purified from fetal fibroblast conditioned medium).

Example 6: Anti-MSF antibody production

Objective: To generate polyclonal antibodies to MSF.

Methods: Rabbits were immunised with a 15-mer synthetic peptide based on the C-terminus of MSF: note, this contains the entire 10 amino acid unique sequence and the contiguous 5 amino sequence of fibronectin. The synthetic peptide was coupled to keyhole limpet haemocyanin (KLH) carrier and used to immunise two rabbits with the following protocol: first injection of 10 mg and second injection of 5 mg three weeks later. Serum was collected six weeks after the first injection and purified IgG shown to recognise the synthetic peptide in both dot and Western blots.

Results: We have used the antibody for both Western blots and immunohistochemistry. The former application has (i) confirmed that rhMSF is recognised by the antibody, and (ii) demonstrated that fetal, but not adult, fibroblasts produce a 70 kDa molecule which is recognised by the antibody and expresses migration stimulating activity when eluted from the PAGE gels.

Polyclonal antibodies were generated against a synthetic peptide incorporating the 10 amino acid "unique" MSF C-terminal sequence. This antibody recognises the unique synthetic peptide (down to 5 ng) and MSF (down to 10 ng) in dot blots; it does not recognise fibronectin or BSA at concentrations up to 4 μg. This antibody has been used to

investigate the tissue distribution of MSF; these experiments show that MSF is present in the stromal compartment of fetal skin and is not detectable in adult skin.

CLAIMS

1. A recombinant polynucleotide encoding a polypeptide comprising the amino acid sequence

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or variants or fragments or derivatives or fusions thereof or fusions of said variants or fragments or derivatives.

2. A polynucleotide according to Claim 1, encoding a polypeptide comprising the amino acid sequence shown in Figure 2 labelled pMSF1α between positions 19 and 660, or variants or fragments or fusions or derivatives thereof or fusions of said variants or fragments or derivatives.

3. A polynucleotide according to Claim 1 or 2, which contains no introns.

4. A polynucleotide according to any one of the preceding claims, comprising the polynucleotide whose sequence is shown in Figure 1.

5. A polynucleotide according to any one of the preceding claims, comprising the polynucleotide whose sequence is shown in Figure 1 between positions 57 and 1982.

6. A polynucleotide according to any one of the preceding claims, encoding a polypeptide which has migration stimulating factor activity.

7. A replicable vector comprising a polynucleotide as defined in any one of Claims 1 to 6.

8. A host cell comprising a recombinant polynucleotide or a replicable vector as defined in any one of Claims 1 to 7.

9. A method of making a polypeptide having the amino acid sequence

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or variants or fragments or fusions or derivatives thereof, or fusions of said variants or fragments or derivatives, the method comprising culturing a host cell as defined in Claim 8 which expresses said variant or fragment

or derivative or fusion and isolating said polypeptide or variant or fragment or derivative or fusion from said host cell culture.

10. A polypeptide comprising the amino acid sequence

```
N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y
```

[SEQ ID NO: 1]

or variants or fragments or fusions or derivatives thereof or fusions of said variants or fragments or derivatives.

11. A polypeptide according to Claim 10, comprising the amino acid sequence shown in Figure 2 labelled pMSF1α between positions 19 and 660, or variants or fragments or fusions thereof or fusions of said variants or fragments.

12. A polypeptide obtainable by the method of Claim 9.

13. A polypeptide according to any one of Claims 10 to 12, which has migration stimulating factor activity.

14. An antibody reactive towards the polypeptide whose amino acid sequence is

```
N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y
```

[SEQ ID NO: 1]

or natural variants thereof but not reactive towards fibronectin.

15. An antibody reactive towards the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α between positions 19 and 660 or natural variants thereof but not reactive towards fibronectin.

16. An antibody reactive towards an epitope present in the polypeptide whose amino acid sequence is

```
N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
```

C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or natural variants thereof but which epitope is not present in fibronectin.

17. An antibody reactive towards an epitope present in the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α between positions 19 and 660 or natural variants thereof but which epitope is not present in fibronectin.

18. An antibody according to any one of Claims 14 to 17, reactive towards a molecule comprising any one of the peptides ISKYILRWRPVSIPPRNLGY [SEQ ID NO: 3] or QQWERTYLGNALVCTCYGGSR [SEQ ID NO: 4] or EPCVLPF-TYNDRTDSTTSNYEQDQ [SEQ ID NO: 14] or CTDHTVLVQTRGGNSNGA-LCH [SEQ ID NO: 15] or VGNGRGEWTCIAYSQLRDQCI [SEQ ID NO: 7].

19. An antibody reactive towards fibronectin but not reactive towards the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or natural variants thereof.

20. An antibody reactive towards fibronectin but not reactive towards the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α between positions 19 and 660 or natural variants thereof.

21. An antibody reactive towards an epitope present in fibronectin but not present in the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or natural variants thereof.

22. An antibody reactive towards an epitope present in fibronectin but not present in the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α between positions 19 and 660 or natural variants thereof.

23. An antibody according to any one of Claims 19 to 22 reactive towards a molecule comprising any one of the peptides

QQWERTYLGNVLVCTCYGGSR [SEQ ID NO: 8] or EPCVLPFTYNGRTFYSCTTEGR-QDGHLWCSTTSNYEQDQ [SEQ ID NO: 9] or CTDHTVLVQTQGGNSNGALCH [SEQ ID NO: 10] or VGNGRGEWTCYAYSQLRDQCI [SEQ ID NO: 11] or ISKYILRWRPKN-SVGRWKEA [SEQ ID NO: 12] or peptides derived from position 648 in fibronectin as shown in Figure 2.

24. An antibody according to any one of Claims 14 to 24 which is a monoclonal antibody.

25. A method of making an antibody which is reactive towards the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof and which is not reactive with fibronectin, the method comprising the steps of, where appropriate, immunising an animal with a peptide which distinguishes MSF from fibronectin and selecting an antibody which binds MSF but does not substantially bind fibronectin.

26. A method of making an antibody which is reactive towards fibronectin and which is not reactive towards the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof, the method comprising the steps of, where appropriate, immunising an animal with a peptide which distinguishes fibronectin from MSF and selecting an antibody which binds fibronectin but does not substantially bind MSF.

27. A molecule which is capable of, following immunisation of an animal if appropriate, giving rise to antibodies which are reactive towards the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F

I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or natural variants thereof but not reactive towards fibronectin.

28. A molecule which is capable of, following immunisation of an animal if appropriate, giving rise to antibodies which are reactive towards fibronectin but not reactive towards the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or natural variants thereof.

29. A molecule according to Claim 27 which is a peptide comprising any one of the sequences

ISKYILRWRPVSIPPRNLGY [SEQ ID NO: 3]; or

QQWERTYLGNALVCTCYGGSR [SEQ ID NO: 4]; or

PCVLPFTYNDRTDSTTSNYEQDQ [SEQ ID NO: 5]; or

TDHTVLVQTRGGNSNGALCH; or [SEQ ID NO: 6]; or

VGNGRGEWTCIAYSQLRDQCI [SEQ ID NO: 7]

which are found in MSF.

30. A molecule according to Claim 28, which is a peptide comprising any one of the sequences

QQWERTYLGNVLVCTCYGGSR [SEQ ID NO: 8] or
EPCVLPFTYNGRTFYSCTTEGRQDGHLWCSTTSNYEQDQ [SEQ ID NO: 9] or
CTDHTVLVQTQGGNSNGALCH [SEQ ID NO: 10] or
VGNGRGEWTCYAYSQLRDQCI [SEQ ID NO: 11] or
ISKYILRWRPKNSVGRWKEA [SEQ ID NO: 12] or

peptides derived from position 648 onwards in fibronectin as shown in Figure 2.

31. A polynucleotide which is capable of distinguishing a polynucleotide which encodes the polypeptide whose sequence is

```
N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y
```

[SEQ ID NO: 1]

or a natural variant thereof and a polynucleotide which encodes fibronectin.

32. A polynucleotide which is capable of hybridising to a polynucleotide which encodes fibronectin but not a polynucleotide which encodes the polypeptide whose sequence is

```
N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y
```

[SEQ ID NO: 1]

or a natural variant thereof.

33. A polynucleotide which is capable of hybridising to a polynucleotide which encodes the polypeptide whose sequence is

```
N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y
```

[SEQ ID NO: 1]

or a natural variant thereof but not to a polynucleotide which encodes fibronectin.

34. A polynucleotide according to any one of Claims 31 to 33, wherein the polynucleotide is an oligonucleotide.

35. A polynucleotide according to any one of Claims 31 to 34, wherein the polynucleotide which encodes fibronectin or the polynucleotide which encodes the polypeptide as said or a natural variant thereof is a mRNA or a cDNA.

36. A method of diagnosing cancer the method comprising detecting in a sample from the person to be diagnosed the presence of a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant or fragment thereof using a reagent which can distinguish said polypeptide from fibronectin.

37. A method of determining susceptibility to cancer the method comprising detecting in a sample derived from the person to be tested the presence of a polypeptide whose sequence is

NLVATCLPVRASLPHRLN
MLRGPGPGLLLLAVQCLGTAVPSTGASKSK
RQAQQMVQPQSPVAVSQSKPGCYDNGKHYQ
INQQWERTYLGNALVCTCYGGSRGFNCESK
PEAEETCFDKYTGNTYRVGDTYERPKDSMI
WDCTCIGAGRGRISCTIANRCHEGGQSYKI
GDTWRRPHETGGYMLECVCLGNGKGEWTCK
PIAEKCFDHAAGTSYVVGETWEKPYQGWMM
VDCTCLGEGSGRITCTSRNRCNDQDTRTSY
RIGDTWSKKDNRGNLLQCICTGNGRGEWKC
ERHTSVQTTSSGSGPFTDVRAAVYQPQPHP
QPPPYGHCVTDSGVVYSVGMQWLKTQGNKQ
MLCTCLGNGVSCQETAVTQTYGGNSNGEPC
VLPFTYNDRTDSTTSNYEQDQKYSFCTDHT
VLVQTRGGNSNGALCHFPFLYNNHNYTDCT
SEGRRDNMKWCGTTQNYDADQKFGFCPMAA
HEEICTTNEGVMYRIGDQWDKQHDMGHMMR
CTCVGNGRGEWTCIAYSQLRDQCIVDDITY
NVNDTFHKRHEEGHMLNCTCFGQGRGRWKC
DPVDQCQDSETGTFYQIGDSWEKYVHGVRY
QCYCYGRGIGEWHCQPLQTYPSSSGPVEVF
ITETPSQPNSHPIQWNAPQPSHISKYILRW
RPVSIPPRNLGY

[SEQ ID NO: 1]

or a natural variant or fragment thereof using a reagent which can distinguish said polypeptide from fibronectin.

38. A method of determining the likely outcome of a patient with cancer the method comprising detecting in a sample from the patient the presence of a polypeptide whose sequence is

NLVATCLPVRASLPHRLN
MLRGPGPGLLLLAVQCLGTAVPSTGASKSK
RQAQQMVQPQSPVAVSQSKPGCYDNGKHYQ
INQQWERTYLGNALVCTCYGGSRGFNCESK
PEAEETCFDKYTGNTYRVGDTYERPKDSMI
WDCTCIGAGRGRISCTIANRCHEGGQSYKI
GDTWRRPHETGGYMLECVCLGNGKGEWTCK
PIAEKCFDHAAGTSYVVGETWEKPYQGWMM
VDCTCLGEGSGRITCTSRNRCNDQDTRTSY
RIGDTWSKKDNRGNLLQCICTGNGRGEWKC
ERHTSVQTTSSGSGPFTDVRAAVYQPQPHP
QPPPYGHCVTDSGVVYSVGMQWLKTQGNKQ
MLCTCLGNGVSCQETAVTQTYGGNSNGEPC
VLPFTYNDRTDSTTSNYEQDQKYSFCTDHT
VLVQTRGGNSNGALCHFPFLYNNHNYTDCT
SEGRRDNMKWCGTTQNYDADQKFGFCPMAA
HEEICTTNEGVMYRIGDQWDKQHDMGHMMR

C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant or fragment thereof using a reagent which can distinguish said polypeptide from fibronectin.

39. A method according to any one of Claims 36 to 38, wherein the reagent which can distinguish said polypeptide from fibronectin is an antibody according to any one of Claims 14 to 18.

40. A method of diagnosing cancer the method comprising detecting in a sample from the person to be diagnosed a polynucleotide encoding a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof using a reagent which can distinguish said polynucleotide from a polynucleotide encoding fibronectin.

41. A method of determining susceptibility to cancer the method comprising detecting in a sample derived from the person to be tested the presence of a polynucleotide encoding a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof using a reagent which can distinguish said polynucleotide from a polynucleotide encoding fibronectin.

42. A method of determining the likely outcome of a patient with cancer the method comprising detecting in a sample from the patient the presence of a polynucleotide encoding a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C

D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof using a reagent which can distinguish said polynucleotide from a polynucleotide encoding fibronectin.

43. A method according to any one of Claims 40 to 42, wherein the reagent which can distinguish said polynucleotide from a polynucleotide encoding fibronectin is a polynucleotide according to Claim 31 or 33.

44. A method according to any one of Claims 36 to 43, wherein the cancer is breast cancer.

45. Use of a reagent which can distinguish the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

[SEQ ID NO: 1]

or a natural variant thereof from fibronectin in the manufacture of a reagent for diagnosing cancer.

46. Use of a reagent as defined in Claim 45, as a diagnostic agent.

47. A method of modulating cell migration the method comprising administering an effective amount of a polypeptide according to any one of Claims 10 to 13 to the site where modulation of cell migration is required.

48. A method according to Claim 47, wherein the cell is a fibroblast or an endothelial cell.

49. A method according to Claim 47 or 48, wherein the site is in a mammalian body.

50. A method according to Claim 49, wherein the site is in a human body.

51. Use of a polypeptide according to any one of Claims 10 to 13, in the manufacture of an agent for modulating cell migration.

52. Use of a polypeptide according to any one of Claims 10 to 13, for modulating cell migration.

53. A method of healing a wound the method comprising administering to the locality of the wound an effective amount of a polypeptide according to any one of Claims 10 to 13.

54. Use of a polypeptide according to any one of Claims 10 to 13, in the manufacture of a medicament for healing wounds.

55. Use of a polypeptide according to any one of Claims 10 to 13, for healing wounds.

56. A pharmaceutical composition comprising a polypeptide according to any one of Claims 10 to 13 and a pharmaceutically acceptable carrier.

57. A polypeptide according to any one of Claims 10 to 13 for use in medicine.

58. A method of preventing scarring comprising administering to the locality of the site where scarring is to be prevented an effective amount of a polypeptide according to any one of Claims 10 to 13.

1/7 [SEQ ID NO: 2]

```
   1  CAAACTTGGT GGCAACTTGC CTCCCGGTGC GGGCGTCTCT CCCCCACCGT
  51  CTCAACATGC TTAGGGGTCC GGGGCCCGGG CTGCTGCTGC TGGCCGTCCA
 101  GTGCCTGGGG ACAGCGGTGC CCTCCACGGG AGCCTCGAAG AGCAAGAGGC
 151  AGGCTCAGCA AATGGTTCAG CCCCAGTCCC CGGTGGCTGT CAGTCAAAGC
 201  AAGCCCGGTT GTTATGACAA TGGAAAACAC TATCAGATAA ATCAACAGTG
 251  GGAGCGGACC TACCTAGGCA ATGCGTTGGT TTGTACTTGT TATGGAGGAA
 301  GCCGAGGTTT TAACTGCGAG AGTAAACCTG AAGCTGAAGA GACTTGCTTT
 351  GACAAGTACA CTGGGAACAC TTACCGAGTG GGTGACACTT ATGAGCGTCC
 401  TAAAGACTCC ATGATCTGGG ACTGTACCTG CATCGGGGCT GGGCGAGGGA
 451  GAATAAGCTG TACCATCGCA AACCGCTGCC ATGAAGGGGG TCAGTCCTAC
 501  AAGATTGGTG ACACCTGGAG GAGACCACAT GAGACTGGTG GTTACATGTT
 551  AGAGTGTGTG TGTCTTGGTA ATGGAAAAGG AGAATGGACC TGCAAGCCCA
 601  TAGCTGAGAA GTGTTTTGAT CATGCTGCTG GGACTTCCTA TGTGGTCGGA
 651  GAAACGTGGG AGAAGCCCTA CCAAGGCTGG ATGATGGTAG ATTGTACTTG
 701  CCTGGGAGAA GGCAGCGGAC GCATCACTTG CACTTCTAGA AATAGATGCA
 751  ACGATCAGGA CACAAGGACA TCCTATAGAA TTGGAGACAC CTGGAGCAAG
 801  AAGGATAATC GAGGAAACCT GCTCCAGTGC ATCTGCACAG GCAACGGCCG
 851  AGGAGAGTGG AAGTGTGAGA GGCACACCTC TGTGCAGACC ACATCGAGCG
 901  GATCTGGCCC CTTCACCGAT GTTCGTGCAG CTGTTTACCA ACCGCAGCCT
 951  CACCCCCAGC CTCCTCCCTA TGGCCACTGT GTCACAGACA GTGGTGTGGT
1001  CTACTCTGTG GGGATGCAGT GGCTGAAGAC ACAAGGAAAT AAGCAAATGC
1051  TTTGCACGTG CCTGGGCAAC GGAGTCAGCT GCCAAGAGAC AGCTGTAACC
```

Fig. 1 (part 1)

1101 CAGACTTACG GTGGCAACTC AAATGGAGAG CCATGTGTCT TACCATTCAC

1151 CTACAACGAC AGGACGGACA GCACAACTTC GAATTATGAG CAGGACCAGA

1201 AATACTCTTT CTGCACAGAC CACACTGTTT TGGTTCAGAC TCGAGGAGGA

1251 AATTCCAATG GTGCCTTGTG CCACTTCCCC TTCCTATACA ACAACCACAA

1301 TTACACTGAT TGCACTTCTG AGGGCAGAAG AGACAACATG AAGTGGTGTG

1351 GGACCACACA GAACTATGAT GCCGACCAGA AGTTTGGGTT CTGCCCCATG

1401 GCTGCCCACG AGGAAATCTG CACAACCAAT GAAGGGGTCA TGTACCGCAT

1451 TGGAGATCAG TGGGATAAGC AGCATGACAT GGGTCACATG ATGAGGTGCA

1501 CGTGTGTTGG GAATGGTCGT GGGGAATGGA CATGCATTGC CTACTCGCAG

1551 CTTCGAGATC AGTGCATTGT TGATGACATC ACTTACAATG TGAACGACAC

1601 ATTCCACAAG CGTCATGAAG AGGGGCACAT GCTGAACTGT ACATGCTTCG

1651 GTCAGGGTCG GGGCAGGTGG AAGTGTGATC CCGTCGACCA ATGCCAGGAT

1701 TCAGAGACTG GGACGTTTTA TCAAATTGGA GATTCATGGG AGAAGTATGT

1751 GCATGGTGTC AGATACCAGT GCTACTGCTA TGGCCGTGGC ATTGGGGAGT

1801 GGCATTGCCA ACCTTTACAG ACCTATCCAA GCTCAAGTGG TCCTGTCGAA

1851 GTATTTATCA CTGAGACTCC GAGTCAGCCC AACTCCCACC CCATCCAGTG

1901 GAATGCACCA CAGCCATCTC ACATTTCCAA GTACATTCTC AGGTGGAGAC

1951 CTGTGAGTAT CCCACCCAGA AACCTTGGAT ACTGAGTCTC CTAATCTTAT

2001 CAATTCTGAT GGTTTCTTTT TTTCCCAGCT TTTGAGCCAA CAACTCTGAT

2051 TAACTATTCC TATAGCATTT ACTATATTTG TTTAGTGAAC AAACAATATG

2101 TGGTCAATTA AATTGACTTG TAGACTGAAA AAAAAAAAAA AAAAAAA

Fig. 1 (part 2)

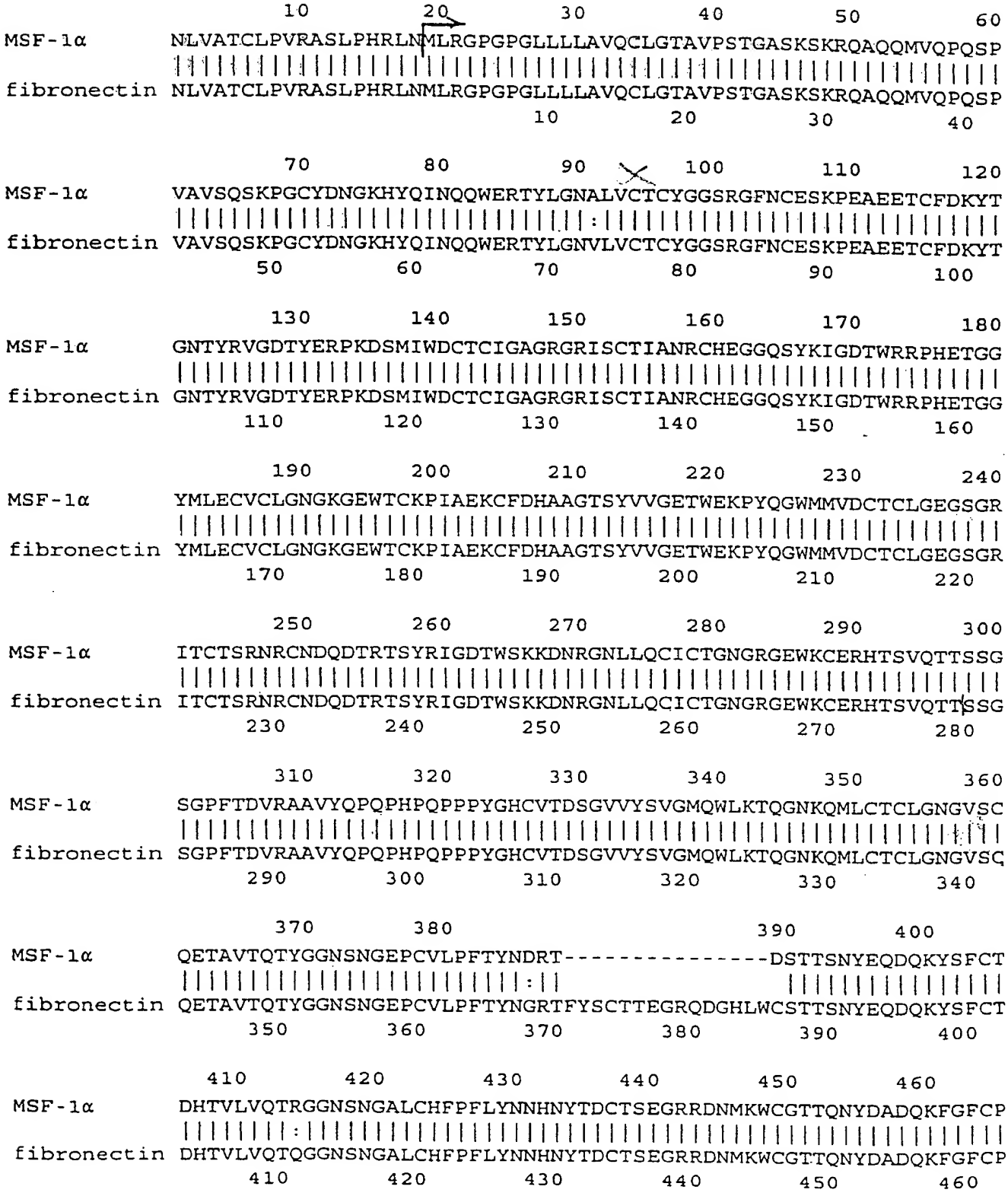
MSF-1α NLVATCLPVRASLPHRLNMLRGPGPGLLLLAVQCLGTAVPSTGASKSKRQAQQMVQPQSP
fibronectin NLVATCLPVRASLPHRLNMLRGPGPGLLLLAVQCLGTAVPSTGASKSKRQAQQMVQPQSP
MSF-1α VAVSQSKPGCYDNGKHYQINQQWERTYLGNALVCTCYGGSRGFNCESKPEAEETCFDKYT
fibronectin VAVSQSKPGCYDNGKHYQINQQWERTYLGNVLVCTCYGGSRGFNCESKPEAEETCFDKYT
MSF-1α GNTYRVGDTYERPKDSMIWDCTCIGAGRGRISCTIANRCHEGGQSYKIGDTWRRPHETGG
fibronectin GNTYRVGDTYERPKDSMIWDCTCIGAGRGRISCTIANRCHEGGQSYKIGDTWRRPHETGG
MSF-1α YMLECVCLGNGKGEWTCKPIAEKCFDHAAGTSYVVGETWEKPYQGWMMVDCTCLGEGSGR
fibronectin YMLECVCLGNGKGEWTCKPIAEKCFDHAAGTSYVVGETWEKPYQGWMMVDCTCLGEGSGR
MSF-1α ITCTSRNRCNDQDTRTSYRIGDTWSKKDNRGNLLQCICTGNGRGEWKCERHTSVQTTSSG
fibronectin ITCTSRNRCNDQDTRTSYRIGDTWSKKDNRGNLLQCICTGNGRGEWKCERHTSVQTTSSG
MSF-1α SGPFTDVRAAVYQPQPHPQPPPYGHCVTDSGVVYSVGMQWLKTQGNKQMLCTCLGNGVSC
fibronectin SGPFTDVRAAVYQPQPHPQPPPYGHCVTDSGVVYSVGMQWLKTQGNKQMLCTCLGNGVSC
MSF-1α QETAVTQTYGGNSNGEPCVLPFTYNDRT----------DSTTSNYEQDQKYSFCT
fibronectin QETAVTQTYGGNSNGEPCVLPFTYNGRTFYSCTTEGRQDGHLWCSTTSNYEQDQKYSFCT
MSF-1α DHTVLVQTRGGNSNGALCHFPFLYNNHNYTDCTSEGRRDNMKWCGTTQNYDADQKFGFCP
fibronectin DHTVLVQTQGGNSNGALCHFPFLYNNHNYTDCTSEGRRDNMKWCGTTQNYDADQKFGFCP

Fig. 2 (part 1)

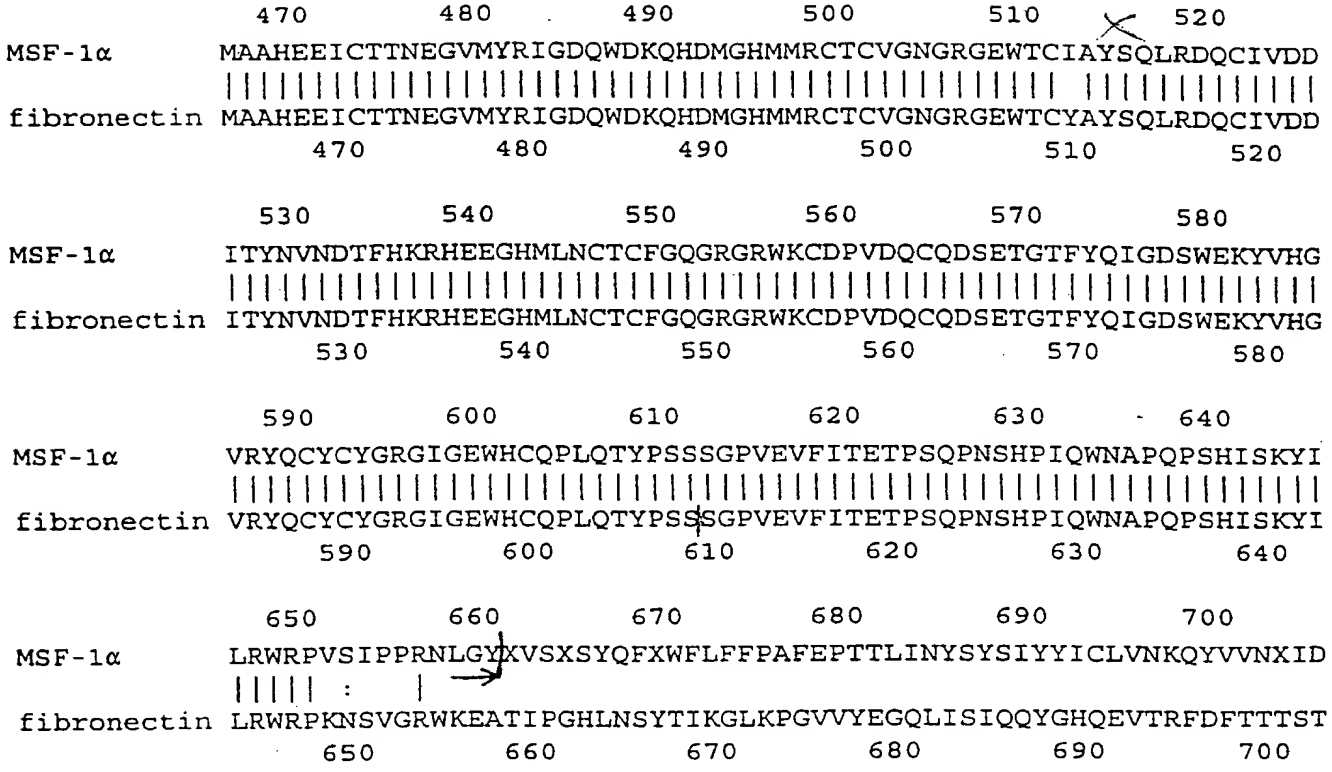
470 480 490 500 510 520
MSF-1α MAAHEEICTTNEGVMYRIGDQWDKQHDMGHMMRCTCVGNGRGEWTCIAYSQLRDQCIVDD
fibronectin MAAHEEICTTNEGVMYRIGDQWDKQHDMGHMMRCTCVGNGRGEWTCYAYSQLRDQCIVDD
470 480 490 500 510 520
530 540 550 560 570 580
MSF-1α ITYNVNDTFHKRHEEGHMLNCTCFGQGRGRWKCDPVDQCQDSETGTFYQIGDSWEKYVHG
fibronectin ITYNVNDTFHKRHEEGHMLNCTCFGQGRGRWKCDPVDQCQDSETGTFYQIGDSWEKYVHG
530 540 550 560 570 580
590 600 610 620 630 640
MSF-1α VRYQCYCYGRGIGEWHCQPLQTYPSSSGPVEVFITETPSQPNSHPIQWNAPQPSHISKYI
fibronectin VRYQCYCYGRGIGEWHCQPLQTYPSSSGPVEVFITETPSQPNSHPIQWNAPQPSHISKYI
590 600 610 620 630 640
650 660 670 680 690 700
MSF-1α LRWRPVSIPPRNLGYXVSXSYQFXWFLFFPAFEPTTLINYSYSIYYICLVNKQYVVNXID
fibronectin LRWRPKNSVGRWKEATIPGHLNSYTIKGLKPGVVYEGQLISIQQYGHQEVTRFDFTTTST
650 660 670 680 690 700

Fig. 2 (part 2)

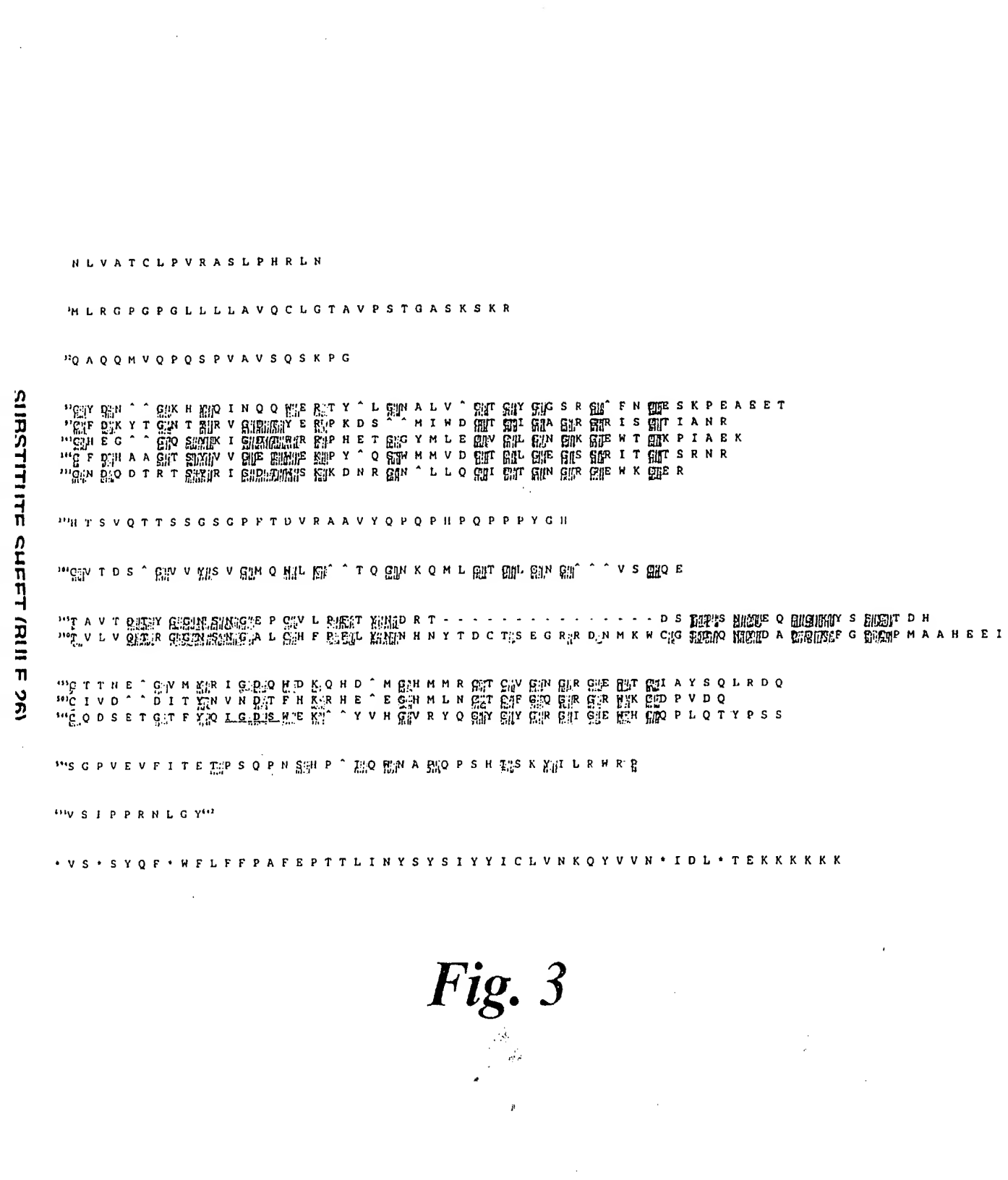

Fig. 3

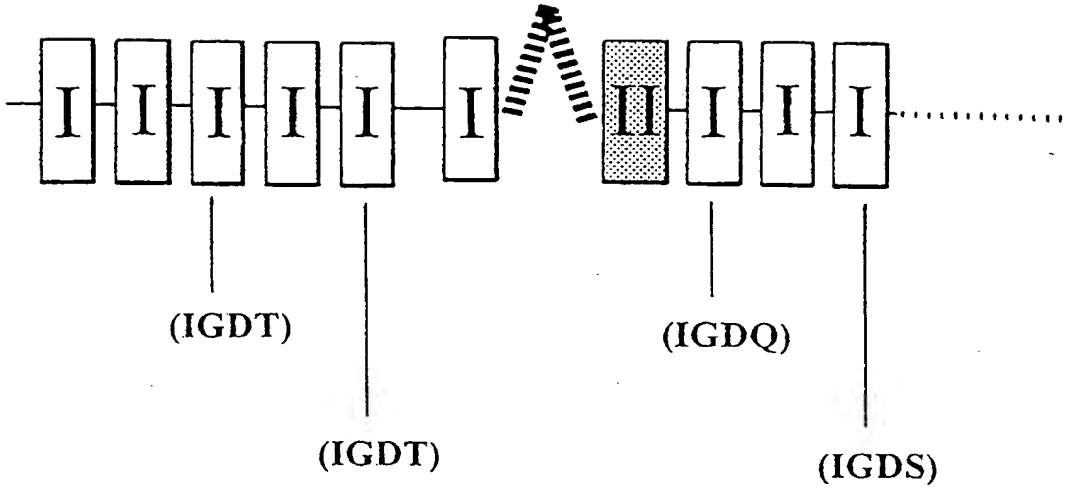

Fig. 4

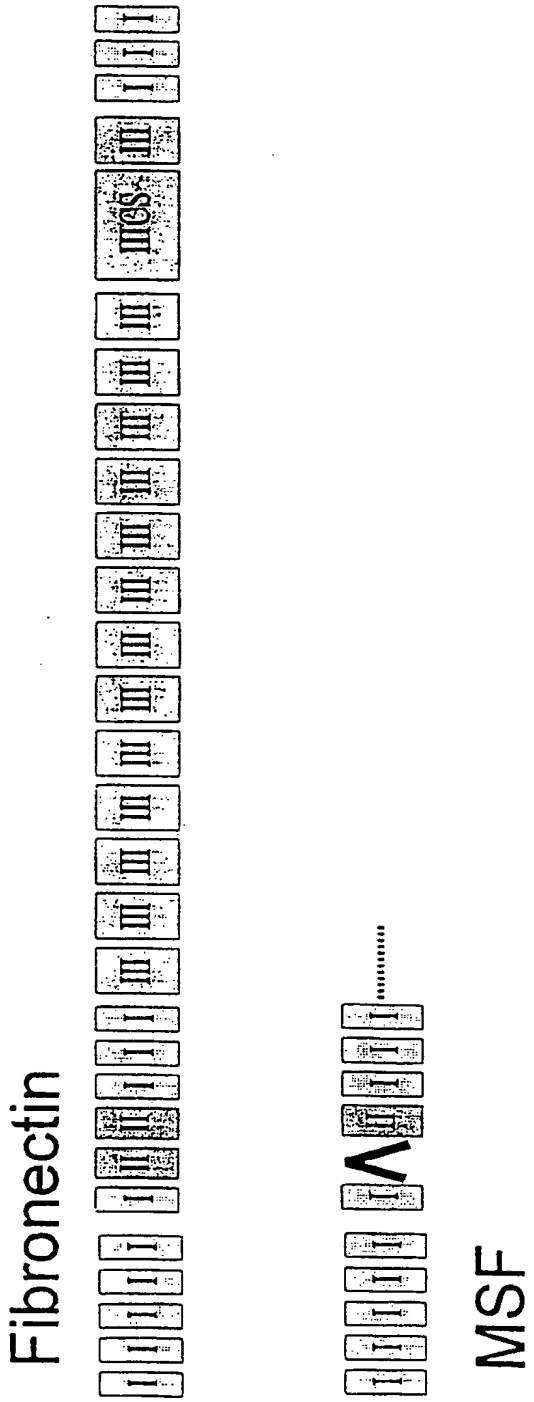

Fig. 5

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
DUNW/P20111PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 98/ 03766	15/12/1998	16/12/1997
Applicant		
UNIVERSITY OF DUNDEE et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03766

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet PCT/ISA/210

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-18, 25, 27, 29, 31, 33 and 36-58 in totality, and 24, 34 and 35 partly

Polynucleotide and polypeptide of migration stimulating factor and their uses, and an antibody reactive with the polypeptide, but not with fibronectin, and the use of the antibody.

2. Claims: 19-23, 26, 28, 30 and 32 in totality, and 24, 34 and 35 partly

An antibody reactive with fibronectin but not with the polypeptide of invention I, and its use.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 47-50, 52, 53, 55 and 58 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/03766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N5/10 C12N15/63 C07K14/78 C07K16/18
C12Q1/68 G01N33/574 A61K38/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 16085 A (ZYMOGENETICS INC) 21 July 1994	1-3, 6-13,27, 29,53-57
A	see abstract; claims see page 2, line 30 - page 4, line 8	4,5,51, 52
A	WO 90 00567 A (CANCER RES CAMPAIGN TECH) 25 January 1990 see page 1 - page 10 -/--	9-18,25, 27,29, 36-39, 44-57

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 May 1999	07/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ceder, O

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KORNBLIHTT ET AL.: "Human mRNA for fibronectin" EMBL SEQUENCE DATABASE,7 November 1985, XP002103220 HEIDELBERG DE Ac X02761 see the whole document	1-3,6
X	-& KORNBLIHTT ET AL.: "Primary structure of human fibronectin: differential splicing may generate at least 10 polypeptides from a single gene" THE EMBO JOURNAL , vol. 4, no. 7, 1985, pages 1755-1759, XP002051533 see abstract see page 1759, left-hand column	1-3,6, 10-13, 27,29
X	KORNBLIHTT ET AL.: "Human fibronectin precursor" SWISSPROT SEQUENCE DATA BASE,21 July 1986, XP002103221 Ac P02751 see the whole document	10-13, 27,29
X	& KORNBLIHTT ET AL.: "Primary structure of human fibronectin: differential splicing may generate at least 10 polypeptides from a single gene" THE EMBO JOURNAL, vol. 4, no. 7, 1985, pages 1755-1759, XP002051533 see abstract see page 1759, left-hand column	1-3,6, 10-13, 27,29
X	EP 0 207 751 A (DELTA BIOTECHNOLOGY LTD) 7 January 1987 see abstract; claims; figures 2,3 see page 13, line 30 - page 15, line 10	1,3, 6-10,12, 13,27,29
X	"Homo sapiens fibronectin splice form ED-A" PIR1 SEQUENCE DATA BASE,27 November 1985, XP002103253 Ac FNHU see the whole document & DEAN ET AL.: "Cloning and analysis of the promoter region of the human fibronectin gene" PROC. NATL. ACAD. SCI. U.S.A., vol. 84, 1987, pages 1876-1880,	10-13, 27,29
X	EP 0 344 134 A (IST NAZ RIC SUL CANCRO) 29 November 1989 see abstract; figure 1	19-24, 26,28,30

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 571 679 A (SEKIGUCHI KIYOTOSHI ET AL) 5 November 1996	14-17, 24,25,27
A	US 5 629 291 A (RUOSLAHTI ERKKI I ET AL) 13 May 1997 see abstract see column 1, line 29 - line 40 see column 1, line 55 - line 57	10,29, 36,47, 48,53-55

INTERNATIONAL SEARCH REPORT

[redacted]mation on patent family members

[redacted]ternational Application No
PCT/GB 98/03766

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9416085 A	21-07-1994	US 5830700 A	03-11-1998
WO 9000567 A	25-01-1990	EP 0423207 A	24-04-1991
		JP 3505732 T	12-12-1991
EP 0207751 A	07-01-1987	AT 58381 T	15-11-1990
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		DK 306386 A	29-12-1986
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		JP 62089699 A	24-04-1987
EP 0344134 A	29-11-1989	AT 100471 T	15-02-1994
		DE 68912403 D	03-03-1994
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US 5571679 A	05-11-1996	EP 0580859 A	02-02-1994
		WO 9217604 A	15-10-1992
US 5629291 A	13-05-1997	US 5453489 A	26-09-1995
		US 5747452 A	05-05-1998
		US 5837813 A	17-11-1998
		AT 152173 T	15-05-1997
		AU 3656893 A	01-09-1993
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		JP 7506342 T	13-07-1995
		NO 942825 A	29-09-1994
		WO 9315203 A	05-08-1993

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DUNW/P20111PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/03766	15/12/1998	16/12/1997
International Patent Classification (IPC) or national classification and IPC		
C12N15/12		
Applicant		
UNIVERSITY OF DUNDEE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 16 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/07/1999	18.04.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Sprinks. M Telephone No. +49 89 2399 8706

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/03766

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-52 as originally filed

Claims, No.:

1-52 as received on 31/03/2000 with letter of 31/03/2000

Drawings, sheets:

1/7-7/7 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☒ the claims, Nos.: 53-58
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to nov lty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18,21,23-25,27,31-52
	No:	Claims	19,20,22,26,28-30
Inventive step (IS)	Yes:	Claims	1-18,21,23-25,27,31-52
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-52
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The following documents (D) are mentioned for the first time in this opinion/report; the numbering will be adhered to in the rest of the procedure:

D1...WO 94 16085 A (ZYMOGENETICS INC) 21 July 1994
D2...EMBO J., vol. 4, no. 7, 1985, pages 1755-1759 (Kornblihtt et al.)
D3...EMBL Data library, database Pir2, accession no. S14428 (fibronectin precursor - rat), 1989 (Hynes et al.) (document cited from the examiner's own knowledge. A copy of the document is annexed to the communication).
D4...EP-A-0 344 134 (IST NAZ RIC SUL CANCRO) 29 November 1989
D5...DATABASE ENTRY, ID: FINC_XENLA, SWISSPROT database, 1 November 1997 (Desimone et al.) (document cited from the examiner's own knowledge and for applicant's information only. A copy of the document is annexed to the communication).
D6...US-A-5 571 679 (SEKIGUCHI KIYOTOSHI ET AL) 5 November 1996

I) Basis of the opinion/report

Unallowable amendments

1) In amended **claims 14-17, 21-23, 26, 27 and 30-37**, filed on 31.03.00, the applicant has attempted to differentiate antibodies and probes etc. for detecting MSF of the present invention from those for detecting fibronectin of the prior art by using phrasing such as "not reactive towards a fibronectin which contains the amino acid sequence FY...WC". However, it should be noted that this expression effectively narrows the disclaimer (i.e.broadens the subject-matter claimed) in a way which is unclear and lacks basis in the application as originally filed. The text upon which the applicant has based these amendments only actually concerns the generation of antibodies against fibronectin, and refers to an oligopeptide sequence of which FY...WC is only a part (see page 24 of the present description).

In any event, as mentioned above, claims containing such a disclaimer would still be considered unclear since the antibodies and probes claimed could still be reactive against a fibronectin with a single amino acid substitution at one of the positions indicated (see for example the fibronectin of D5).

Consequently, said claims have been interpreted as if the disclaimer only referred to fibronectin in general.

V) Reasoned statement

Novelty

1) The present application does not satisfy the criterion set forth in **Article 33 (2) PCT** because the subject-matter of **claims 19, 20, 22, 26 and 28-30** is not new in respect of prior art as defined in the regulations (**Rule 64.1 - 64.3 PCT**).

2) Said claims refer to antibodies and probes which are characterised only by their ability to react or hybridise with fibronectin polypeptides and polynucleotides of the prior art but not with the MSF polypeptides and polynucleotides of the present invention. Consequently, in view of the fact that antibodies and probes reactive or hybridising with fibronectin and its other splice variants are disclosed throughout the prior art (e.g. D1-D6) and that MSF polypeptide and polynucleotide sequences were not available before the priority date of the present application, this definition alone must, for the time being, be considered insufficient to establish the novelty of the claimed antibodies and probes over those of said documents.

If, however, at a later date, comparative studies were to demonstrate that the antibodies and probes claimed are indeed novel, they might also be considered unitary with the other subject-matter claimed, since a broad unifying and inventive concept such as "differentiating MSF from fibronectin" might be acknowledged (method claims referring to the use of MSF polypeptides and polynucleotides for screening fibronectin/non-MSF-reactive antibodies and probes might be another alternative).

Novelty, inventive step and industrial applicability

3) **Claims 1-18, 21, 23-25, 27 and 31-52** are considered to fulfil the criteria of **Article 33 (2) - (4) PCT** since, in the light of the available prior art, they define what appears to be new, inventive and industrially applicable concept, namely a splice variant of fibronectin (MSF), defined by its sequence in SEQ ID NO:1 and

encoded by the nucleotide sequence of SEQ ID NO:2 (as well as variants thereof differing only in the usage of the genetic code).

Nevertheless, particular attention should be paid to the objections concerning lack of clarity made in section VIII below.

Industrial applicability

4) For the assessment of the subject-matter of present **claims 41-44, 46, 47, 49 and 52** (as far as *in vivo* methods are concerned) on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VIII) Certain observations

Insufficiency of disclosure and clarity

1) The present application does not satisfy the criterion set forth in **Articles 5 and 6 PCT** because the subject-matter of **claims 1-4, 11, 14-19, 21-23, 26, 27, 30-32 and 34-37** is insufficiently disclosed and/or unclear.

2) As mentioned in section V above, the invention appears to centre around one particular fibronectin splice variant, MSF. Consequently, use of the open-ended term "encoding" in **claim 1** causes considerable problems with regard to the clarity and sufficiency of disclosure of the subject-matter of **claims 1-4** for the following reasons:

D2 discloses that fibronectin and other splice variants thereof with MSF activity were known in the prior art and that all are encoded by a common fibronectin gene - a point confirmed on page 4 of the present application. As a result, claims broadly directed to a(ny) polynucleotide encoding one fibronectin variant also

encompass the full length fibronectin gene and unspliced mRNA which also encodes all the others! Whether the polynucleotide is said to be "recombinant" or not is irrelevant - the present claims cover subject-matter which goes far beyond the inventive concept of the present invention and is not unitary with it. In order to fulfil the requirements of the PCT with regard to clarity and sufficiency of disclosure, the scope of protection sought should be commensurate with the technical contribution which the application as a whole makes to the art.

In this case, the applicant has only isolated one specific fibronectin variant and one polynucleotide sequence which encodes it - the claims should reflect this.

3) **Claims 2, 3, 11 and 30-32** still refer to unspecified "variants", fragments", "derivatives" and "fusions" which need not retain any of the properties which characterise the polynucleotides or polypeptides to which they ultimately refer.

4) "Fibronectin" is itself a vague term (D2 highlights this point describing fibronectins as a class of proteins), such that even MSF of the present invention could be considered to be a "fibronectin", bringing the clarity, novelty and overall relevance of claims simply referring to "fibronectin" into question.

5) In order to be clearly defined and belong to the inventive concept of the present invention, all the antibodies referred to in **claims 14-19 and 21-23** would need to be specific for the polypeptide against which they were raised. Otherwise, said claims may be considered to cover cross-reacting antibodies of the prior art.

Similarly, **claims 26 and 27** are unclear because the "stringent hybridization conditions" mentioned in the claims are not precisely defined therein. It is therefore left entirely up to third parties to decide which particular conditions to use.

6) **Claims 30-32 and 34-37** are unclear because they refer to methods for detecting MSF using antibodies and probes which detect fibronectin (see claim dependencies).

CLAIMS

1. A recombinant polynucleotide encoding a polypeptide consisting of (1) the amino acid sequence

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or consisting of (2) a variant or fragment or derivative of said amino acid sequence which has migration stimulating factor activity and which includes the amino acid sequence VSIPPRNLGY, PCVLPFTYNDRTD, DRTDSTTSNYEQDQ, TDHTVLVQTR and/or REGNSNGALCH.

2. A polynucleotide according to Claim 1, wherein the polypeptide consists of the amino acid sequence shown in Figure 2 labelled pMSF1α between positions 19 and 660, or a variant or fragment or derivative of said amino acid sequence.

3. A recombinant polynucleotide encoding a fusion of a polypeptide as defined in Claim 1 or 2 and another polypeptide.

4. A polynucleotide according to Claim 1 or 2, which contains no introns.

5. A polynucleotide according to any one of the preceding claims, comprising the polynucleotide whose sequence is shown in Figure 1.

6. A polynucleotide according to any one of the preceding claims, comprising the polynucleotide whose sequence is shown in Figure 1 between positions 57 and 1982.

7. A replicable vector comprising a polynucleotide as defined in any one of Claims 1 to 6.

8. A host cell comprising a recombinant polynucleotide or a replicable vector as defined in any one of Claims 1 to 7.

9. A method of making a polypeptide as defined in Claim 1 or 2 or a fusion of said polypeptide and another polypeptide the method comprising culturing a host cell as defined in Claim 8 which expresses said polypeptide or fusion and isolating said polypeptide or fusion from said host cell culture.

10. A polypeptide consisting of (1) the amino acid sequence

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C

E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or consisting of (2) a variant or fragment or derivative of said amino acid sequence which has migration stimulating factor activity and which includes the amino acid sequence VSIPPRNLGY, PCVLPFTYNDRTD, DRTDSTTSNYEQDQ, TDHTVLVQTR and/or REGNSNGALCH.

11. A polypeptide according to Claim 10, consisting of the amino acid sequence shown in Figure 2 labelled pMSF1α between positions 19 and 660, or a variant or fragment or derivative of said amino acid sequence.

12. A fusion of a polypeptide according to Claim 10 or 11 and another polypeptide.

13. A polypeptide obtainable by the method of Claim 9.

14. An antibody reactive towards the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K

P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

but not reactive towards a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC.

15. An antibody reactive towards the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α between positions 19 and 660 but not reactive towards a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC.

16. An antibody reactive towards an epitope present in the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y

N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

but which epitope is not present in a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC.

17. An antibody reactive towards an epitope present in the polypeptide whose amino acid sequence is shown in Figure 2 labelled pMSF1α between positions 19 and 660 but which epitope is not present in a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC.

18. An antibody according to any one of Claims 14 to 17, reactive towards a molecule comprising any one of the peptides ISKYILRWRPVSIPPRNLGY or EPCVLPFTYNDRTDSTTSNYEQDQ or CTDHTVLVQTRGGNS-NGALCH.

19. An antibody reactive towards any one of the peptides QQWERTYLGNVLVCTCYGGSR or EPCVLPFTYNGRTFYSCTTEG-RQDGHLWCSTTSNYEQDQ or CTDHTVLVQTQGGNSNGALCH or VGNGRGEWTCYAYSQLRDQCI or ISKYILRWRPKNSVGRWKEA.

20. An antibody according to any one of Claims 14 to 19 which is a monoclonal antibody.

21. A method of making an antibody which is reactive towards the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

(MSF) and which is not reactive with a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC, the method comprising the steps of, where appropriate, immunising an animal with a peptide which distinguishes MSF from a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC and selecting an antibody which binds MSF but does not substantially bind a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC.

22. A method of making an antibody which is reactive towards fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC and which is not reactive towards the polypeptide whose amino acid sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y

R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

(MSF), the method comprising the steps of, where appropriate, immunising an animal with a peptide which distinguishes a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC from MSF and selecting an antibody which binds a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC but does not substantially bind MSF.

23. A molecule which is capable of, following immunisation of an animal if appropriate, giving rise to antibodies which are reactive towards the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W

R P V S I P P R N L G Y

but not reactive towards a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC.

24. A peptide consisting of any one of the sequences
QQWERTYLGNVLVCTCYGGSR or
EPCVLPFTYNGRTFYSCTTEGRQDGHLWCSTTSNYEQDQ or
CTDHTVLVQTQGGNSNGALCH or
VGNGRGEWTCYAYSQLRDQCI or
ISKYILRWRPKNSVGRWKEA.

25. A molecule according to Claim 23 which is a peptide comprising any one of the sequences
ISKYILRWRPVSIPPRNLGY; or
PCVLPFTYNDRTDSTTSNYEQDQ; or
TDHTVLVQTRGGNSNGALCH; or
which are found in MSF.

26. A polynucleotide which is capable of hybridising at high stringency to a polynucleotide which encodes a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC but not a polynucleotide which encodes the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P

Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

27. A polynucleotide which is capable of hybridising at high stringency to a polynucleotide which encodes the polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

but not to a polynucleotide which encodes a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC.

28. A polynucleotide according to any one of Claims 26 to 27, wherein the polynucleotide is an oligonucleotide.

29. A polynucleotide according to any one of Claims 26 to 28, wherein the polynucleotide which encodes a fibronectin or the polynucleotide which encodes the polypeptide as said is a mRNA or a cDNA.

30. A method of diagnosing cancer the method comprising detecting in a sample from the person to be diagnosed the presence of a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or a natural variant containing the amino acid sequence VSIPPRNLGY, PCVLPFTYNDRTD, DRTDSTTSNYEQDQ, TDHTVLVQTR and/or REGNSNGALCH or fragment thereof using a reagent which can distinguish said polypeptide from a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC wherein said reagent is an antibody according to any one of Claims 14 to 20.

31. A method of determining susceptibility to cancer the method comprising detecting in a sample derived from the person to be tested the presence of a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or a natural variant containing the amino acid sequence VSIPPRNLGY, PCVLPFTYNDRTD, DRTDSTTSNYEQDQ, TDHTVLVQTR and/or REGNSNGALCH or fragment thereof using a reagent which can distinguish said polypeptide from a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC wherein said reagent is an antibody according to any one of Claims 14 to 20.

32. A method of determining the likely outcome of a patient with cancer the method comprising detecting in a sample from the patient the presence of a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I

W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or a natural variant containing the amino acid sequence VSIPPRNLGY, PCVLPFTYNDRTD, DRTVSTTSNYEQDQ, TDHTVLVQTR and/or REGNSNGALCH, or fragment thereof using a reagent which can distinguish said polypeptide from a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC wherein said reagent is an antibody according to any one of Claims 14 to 20.

33. A method according to any one of Claims 30 to 32, wherein the reagent which can distinguish said polypeptide from a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC is an antibody according to any one of Claims 14 to 18.

34. A method of diagnosing cancer the method comprising detecting in a sample from the person to be diagnosed a polynucleotide encoding a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I

C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or a natural variant thereof containing the amino acid sequence VSIPPRNLGY, PCVLPFTYNDRTD, DRTVSTTSNYEQDQ, TDHTVLVQTR and/or REGNSNGALCH, using a reagent which can distinguish said polynucleotide from a polynucleotide encoding a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC wherein said reagent is a polynucleotide according to any one of Claims 26 to 29.

36. A method of determining the likely outcome of a patient with cancer the method comprising detecting in a sample from the patient the presence of a polynucleotide encoding a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or a natural variant thereof containing the amino acid sequence VSIPPRNLGY, PCVLPFTYNDRTD, DRTVSTTSNYEQDQ,

G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R
C T C V G N G R G E W T C I A Y S Q L R D Q C I V D D I T Y
N V N D T F H K R H E E G H M L N C T C F G Q G R G R W K C
D P V D Q C Q D S E T G T F Y Q I G D S W E K Y V H G V R Y
Q C Y C Y G R G I G E W H C Q P L Q T Y P S S S G P V E V F
I T E T P S Q P N S H P I Q W N A P Q P S H I S K Y I L R W
R P V S I P P R N L G Y

or a natural variant thereof containing the amino acid sequence VSIPPRNLGY, PCVLPFTYNDRTD, DRTVSTTSNYEQDQ, TDHTVLVQTR and/or REGNSNGALCH, using a reagent which can distinguish said polynucleotide from a polynucleotide encoding a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC wherein said reagent is a polynucleotide according to any one of Claims 26 to 29.

35. A method of determining susceptibility to cancer the method comprising detecting in a sample derived from the person to be tested the presence of a polynucleotide encoding a polypeptide whose sequence is

N L V A T C L P V R A S L P H R L N
M L R G P G P G L L L L A V Q C L G T A V P S T G A S K S K
R Q A Q Q M V Q P Q S P V A V S Q S K P G C Y D N G K H Y Q
I N Q Q W E R T Y L G N A L V C T C Y G G S R G F N C E S K
P E A E E T C F D K Y T G N T Y R V G D T Y E R P K D S M I
W D C T C I G A G R G R I S C T I A N R C H E G G Q S Y K I
G D T W R R P H E T G G Y M L E C V C L G N G K G E W T C K
P I A E K C F D H A A G T S Y V V G E T W E K P Y Q G W M M
V D C T C L G E G S G R I T C T S R N R C N D Q D T R T S Y
R I G D T W S K K D N R G N L L Q C I C T G N G R G E W K C
E R H T S V Q T T S S G S G P F T D V R A A V Y Q P Q P H P
Q P P P Y G H C V T D S G V V Y S V G M Q W L K T Q G N K Q
M L C T C L G N G V S C Q E T A V T Q T Y G G N S N G E P C
V L P F T Y N D R T D S T T S N Y E Q D Q K Y S F C T D H T
V L V Q T R G G N S N G A L C H F P F L Y N N H N Y T D C T
S E G R R D N M K W C G T T Q N Y D A D Q K F G F C P M A A
H E E I C T T N E G V M Y R I G D Q W D K Q H D M G H M M R

TDHTVLVQTR and/or REGNSNGALCH, using a reagent which can distinguish said polynucleotide from a polynucleotide encoding a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC wherein said reagent is a polynucleotide according to any one of Claims 26 to 29.

37. A method according to any one of Claims 34 to 36, wherein the reagent which can distinguish said polynucleotide from a polynucleotide encoding a fibronectin which contains the amino acid sequence FYSCTTEGRQDGHLWC is a polynucleotide according to Claim 28.

38. A method according to any one of Claims 30 to 37, wherein the cancer is breast cancer.

39. Use of a reagent as defined in any one of Claims 30 to 33in the manufacture of a reagent for diagnosing cancer.

40. Use of a reagent as defined in Claim 39, as a diagnostic agent.

41. A method of modulating cell migration the method comprising administering an effective amount of a polypeptide according to any one of Claims 10 to 13 to the site where modulation of cell migration is required.

42. A method according to Claim 41, wherein the cell is a fibroblast or an endothelial cell.

43. A method according to Claim 41 or 42, wherein the site is in a mammalian body.

44. A method according to Claim 43, wherein the site is in a human body.

45. Use of a polypeptide according to any one of Claims 10 to 13, in the manufacture of an agent for modulating cell migration.

46. Use of a polypeptide according to any one of Claims 10 to 13, for modulating cell migration.

47. A method of healing a wound the method comprising administering to the locality of the wound an effective amount of a polypeptide according to any one of Claims 10 to 13.

48. Use of a polypeptide according to any one of Claims 10 to 13, in the manufacture of a medicament for healing wounds.

49. Use of a polypeptide according to any one of Claims 10 to 13, for healing wounds.

50. A pharmaceutical composition comprising a polypeptide according to any one of Claims 10 to 13 and a pharmaceutically acceptable carrier.

51. A polypeptide according to any one of Claims 10 to 13 for use in medicine.

52. A method of preventing scarring comprising administering to the locality of the site where scarring is to be prevented an effective amount of a polypeptide according to any one of Claims 10 to 13.

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ID   FINC_XENLA     STANDARD;      PRT;  2481 AA.
AC   Q91740;
DT   01-NOV-1997 (Rel. 35, Created)
DT   01-NOV-1997 (Rel. 35, Last sequence update)
DT   15-JUL-1999 (Rel. 38, Last annotation update)
DE   FIBRONECTIN PRECURSOR.
GN   FN1.
OS   Xenopus laevis (African clawed frog).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Amphibia; Batrachia; Anura; Mesobatrachia; Pipoidea; Pipidae;
OC   Xenopodinae; Xenopus.
RN   [1]
RP   SEQUENCE FROM N.A.
RX   MEDLINE; 92111942.
RA   Desimone D.W., Norton P.A., Hynes R.O.;
RT   "Identification and characterization of alternatively spliced
RT   fibronectin mRNAs expressed in early Xenopus embryos.";
RL   Dev. Biol. 149:357-369(1992).
CC   -!- FUNCTION: FIBRONECTINS BIND CELL SURFACES AND VARIOUS COMPOUNDS
CC       INCLUDING COLLAGEN, FIBRIN, HEPARIN, DNA, AND ACTIN. FIBRONECTINS
CC       ARE INVOLVED IN CELL ADHESION, CELL MOTILITY, OPSONIZATION, WOUND
CC       HEALING, AND MAINTENANCE OF CELL SHAPE (BY SIMILARITY).
CC   -!- SUBUNIT: DIMERS OR MULTIMERS OF ALTERNATIVELY SPLICED VARIANTS,
CC       CONNECTED BY 2 DISULFIDE BONDS NEAR THE CARBOXYL ENDS (BY
CC       SIMILARITY).
CC   -!- ALTERNATIVE PRODUCTS: EACH OF THE "EXTRA DOMAIN" & THE CONNECTING
CC       STRAND 3 ARE PRESENT IN SOME FORMS OF FIBRONECTIN AND ABSENT IN
CC       OTHERS. THESE DIFFERENCES ARE DUE TO ALTERNATIVE SPLICING.
CC   -!- TISSUE SPECIFICITY: IN EARLY XENOPUS EMBRYO, CELLULAR FORMS OF
CC       FIBRONECTIN PREDOMINATE WHICH INCLUDE BOTH EXTRA DOMAINS. IN
CC       FIBRONECTIN OF EMBRYONIC AND ADULT LIVER THE CONNECTING STRAND 3
CC       CAN BE EITHER COMPLETELY EXCLUDED OR INCLUDED.
CC   -!- SIMILARITY: CONTAINS 12 FIBRONECTIN TYPE I DOMAINS.
CC   -!- SIMILARITY: CONTAINS 2 FIBRONECTIN TYPE II DOMAINS.
CC   -!- SIMILARITY: CONTAINS 17 FIBRONECTIN TYPE III DOMAINS.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
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CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; M77820; AAA49707.1; -.
DR   HSSP; P02751; 2FN2.
DR   PFAM; PF00039; fn1; 12.
DR   PFAM; PF00040; fn2; 2.
DR   PFAM; PF00041; fn3; 17.
DR   PRINTS; PR00012; FNTYPEI.
DR   PRINTS; PR00013; FNTYPEII.
DR   PRINTS; PR00014; FNTYPEIII.
DR   PROSITE; PS00022; EGF_1; 2.
DR   PROSITE; PS01253; FIBRONECTIN_1; 11.
KW   Glycoprotein; Plasma; Heparin-binding; Acute phase; Cell adhesion;
KW   Repeat; Alternative splicing; Signal.
FT   SIGNAL        1     31       POTENTIAL.
FT   CHAIN        32   2481       FIBRONECTIN.
FT   DOMAIN       55    275       FIBRIN- AND HEPARIN-BINDING 1.
FT   DOMAIN      309    609       COLLAGEN-BINDING.
FT   DNA_BIND    907   1172       BY SIMILARITY.
FT   DOMAIN     1358   1631       CELL-ATTACHMENT.
FT   DOMAIN     1812   2082       HEPARIN-BINDING 2.
FT   DOMAIN     2301   2432       FIBRIN-BINDING 2.
FT   DOMAIN       53     93       FIBRONECTIN TYPE-I 1.
FT   DOMAIN       98    141       FIBRONECTIN TYPE-I 2.
FT   DOMAIN      142    185       FIBRONECTIN TYPE-I 3.
FT   DOMAIN      187    231       FIBRONECTIN TYPE-I 4.
FT   DOMAIN      232    276       FIBRONECTIN TYPE-I 5.
FT   DOMAIN      307    346       FIBRONECTIN TYPE-I 6.
FT   DOMAIN      346    405       FIBRONECTIN TYPE-II 1.
FT   DOMAIN      406    470       FIBRONECTIN TYPE-II 2.
FT   DOMAIN      469    512       FIBRONECTIN TYPE-I 7.
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FT	DOMAIN	517	559	FIBRONECTIN TYPE-I 8.
FT	DOMAIN	560	603	FIBRONECTIN TYPE-I 9.
FT	DOMAIN	610	707	FIBRONECTIN TYPE-III 1.
FT	DOMAIN	708	809	FIBRONECTIN TYPE-III 2.
FT	DOMAIN	810	904	FIBRONECTIN TYPE-III 3.
FT	DOMAIN	905	995	FIBRONECTIN TYPE-III 4.
FT	DOMAIN	996	1085	FIBRONECTIN TYPE-III 5.
FT	DOMAIN	1086	1173	FIBRONECTIN TYPE-III 6.
FT	DOMAIN	1174	1265	FIBRONECTIN TYPE-III 7.
FT	DOMAIN	1266	1356	FIBRONECTIN TYPE-III 8 (EXTRA DOMAIN).
FT	DOMAIN	1357	1447	FIBRONECTIN TYPE-III 9.
FT	DOMAIN	1448	1537	FIBRONECTIN TYPE-III 10.
FT	DOMAIN	1538	1631	FIBRONECTIN TYPE-III 11.
FT	DOMAIN	1632	1721	FIBRONECTIN TYPE-III 12.
FT	DOMAIN	1722	1811	FIBRONECTIN TYPE-III 13 (EXTRA DOMAIN).
FT	DOMAIN	1812	1903	FIBRONECTIN TYPE-III 14.
FT	DOMAIN	1904	1992	FIBRONECTIN TYPE-III 15.
FT	DOMAIN	1993	2082	FIBRONECTIN TYPE-III 16.
FT	DOMAIN	2083	2205	CONNECTING STRAND 3 (CS-3) (V REGION).
FT	DOMAIN	2206	2287	FIBRONECTIN TYPE-III 17.
FT	DOMAIN	2299	2343	FIBRONECTIN TYPE-I 10.
FT	DOMAIN	2344	2386	FIBRONECTIN TYPE-I 11.
FT	DOMAIN	2388	2431	FIBRONECTIN TYPE-I 12.
FT	SITE	1615	1617	CELL ATTACHMENT SITE.
FT	DISULFID	55	81	BY SIMILARITY.
FT	DISULFID	79	90	BY SIMILARITY.
FT	DISULFID	100	128	BY SIMILARITY.
FT	DISULFID	126	138	BY SIMILARITY.
FT	DISULFID	144	172	BY SIMILARITY.
FT	DISULFID	170	182	BY SIMILARITY.
FT	DISULFID	189	218	BY SIMILARITY.
FT	DISULFID	216	228	BY SIMILARITY.
FT	DISULFID	234	263	BY SIMILARITY.
FT	DISULFID	261	273	BY SIMILARITY.
FT	DISULFID	309	336	BY SIMILARITY.
FT	DISULFID	334	343	BY SIMILARITY.
FT	DISULFID	361	387	BY SIMILARITY.
FT	DISULFID	375	402	BY SIMILARITY.
FT	DISULFID	421	447	BY SIMILARITY.
FT	DISULFID	471	499	BY SIMILARITY.
FT	DISULFID	497	509	BY SIMILARITY.
FT	DISULFID	519	546	BY SIMILARITY.
FT	DISULFID	544	556	BY SIMILARITY.
FT	DISULFID	562	590	BY SIMILARITY.
FT	DISULFID	588	600	BY SIMILARITY.
FT	DISULFID	2301	2330	BY SIMILARITY.
FT	DISULFID	2328	2340	BY SIMILARITY.
FT	DISULFID	2346	2373	BY SIMILARITY.
FT	DISULFID	2371	2383	BY SIMILARITY.
FT	DISULFID	2390	2414	BY SIMILARITY.
FT	DISULFID	2412	2428	BY SIMILARITY.
FT	DISULFID	2459	2459	INTERCHAIN (WITH 2463 OF OTHER CHAIN) (BY SIMILARITY).
FT	DISULFID	2463	2463	INTERCHAIN (WITH 2459 OF OTHER CHAIN) (BY SIMILARITY).
FT	CARBOHYD	431	431	POTENTIAL.
FT	CARBOHYD	529	529	POTENTIAL.
FT	CARBOHYD	543	543	POTENTIAL.
FT	CARBOHYD	877	877	POTENTIAL.
FT	CARBOHYD	1244	1244	POTENTIAL.
FT	CARBOHYD	1291	1291	POTENTIAL.
FT	CARBOHYD	2202	2202	POTENTIAL.

SQ SEQUENCE 2481 AA; 272678 MW; 7E47DF4F6CE72C93 CRC64;

MRRGALTGLL LVLCLSVVLR AAPSATSKKR RQAQQQQQQQ VVQPQGTQDN HQKGCYDNGK
YYQINQQWER TYLGNTLVCT CYGGGRGFNC ESKPESEETC FDKYTGVSYR VGETYERPKD
NMIWDCTCIG AGRGRISCTI ANRCHEGGQS YKIGDTWRRP HETGGYMLEC VCLGNGKGEW
TCKPVAERCY DNTAGTSYVV GQTWEKPYQG WMMVDCTCLG EGNGRITCSS KNRCNDQDTK
TSYRIGDTWS KTDTRGNLLQ CICTGNGRGE WKCERHSSAQ ATGTGSNPIT NIQTALYQPD
SQLEPYGHCV TDNGVLYSLG MRWLRTQGSK QMLCTCLGNG VSCEETVATI TFGGNANGEP
CAIPFTHDGK TYYSCTSEGR QDGKLWCATT SNYDSDKKYS FCTEQLALVQ TRGGNSNGAL
CNFPPLYNNL NYTDSTSEGR QDSMKWCGTT ANYDADQKFG FCPMAAHEEI CTTNEGVMYR
VGDQWDKQHD QGHMMRCTCV GNGRGEWSCV AYSQLKDQCI VDGLTYNVNS SFTKLHEEGH
MMNCTCFGQG RGRWKCDAID QCQDTETRQF YQIGDSWEKH LQGVQYQCYC YGKGIGEWHC
QPLSTSQAGT GPVQVIITES ANFPTSHPIQ WNAPQASHIK NYILRWKPKL KAGPWKQATI
PGHLNSYTIS GLKPGILYEG QLISILQYGN REVTTFDFTT TTTIHRHSQT ESGETTPLPP
LVSISESVTE ITASSFLVSW VSASDTVSGF RVEYELSEDG DEKRYLELPN TATSVNIPDL
LPGRRYNVNV YQITEEGEKS LILSTTQTTA PDAPPEHNVE NVDDTSIMIK WNKPQAPITG
YRVVYSPSVE GSSTELNLPS TANSVTLTEL LPGIEYNITI YAVEDSLESV PVFIQQGTTG
TPQTVIVPSP TDLQLVEVTD VKIIIMWTSP QSEVSGYRVV VKPVSPAGRD VQNLPVNRNT
FAEVVNLQPG RTYSFEVYAV NRGQESEPLV GEFATKLDAP TDLQFTDVTE STVVIIWIPP

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     VPSTLEPVGS IPHYNTEVTE T[redacted]TPV PRIGFKLDVR PSQGGEAPRE VISESGSIVI[redacted]
     SGLTPGVEYT YSISVLTDGV E[redacted]TKTV VTPLSPPTNL RLQPSRDSAT LTVYWDRSIS
     PGITGYRIST TPTPMQVGNS LEEEVGPSQT YCVFENLSPG VEYNVSVYAV KEEEESAPLS
     QMFLQEIPQL TDIKYDDVTD TSIDLRWTPL NSSNIIGYRI TVVAAGESVP IYEEFVGPTD
     GYYKVSGLEP GIDYEISLIT LINGGESAPT TIIQHTAVPP PTNLRFTNIG PDNIRVTWSP
     PTSIELSSYL VRYSPVKKPD DVTELSLSPS TNMVVLSNLL PFTEYLVSVH SVYEERESSS
     LNGVARTHLD SPTGIAFSEI TPNSFTVHWI APRGPITGYR IRYQLESGAG RPKEERVPPS
     RNSITLTHLI PGSEYLVSII AINGQQESLP LAGQQATVSD VPTDLEVTSS SPNTLTISWE
     APAVSVRYYR ITYSQTGGHG PREFTVPGT SNTATIRGLN PGVSYTITVY AVTGRGDSPA
     SSKPLTIIHK TDVDQPIDMA VTDIQDHSIH VKWSPPPGPV TGYRVTSVPK SGQGETFSQV
     ISPDQTEVTI VGLQPAVEYV VSIYSQGENG ESEPLVETAV TNIDNPKGLT FTDVGVDSIR
     LAWEVPDGQV TRYRVTYSSP EDGVKELFPA PEGDDDTAEL HGLRPGTEYT VSIVALHDDM
     ESKPLIGIQS TAIPAPTNLQ FSQVTPSGFS LSWHAPTVHL TGYLVRVNPK EKTGPTKEVR
     LSPGVAATTV TGLMVATKYE VNVYALKDSL TSQPLQGLIS TLDNVSPPRR PRIQDVTETT
     VTLSWRTKTE TITGFQIDAI PADGQNPIRR TVDADLRTFT ITGLQPGTDY KIYLYTLNDN
     ARSSPVTVDV TTAVDSPSNL RFLTTTSNSL LFTWQPPRAR ITGYIIRYEK AGGLIKEHLP
     RLPAGTTEST LTNLEPGTEY IIYIIAVRNN MKSEPLVGRK RTDELPRLVT LPHPGQGPEI
     LDVPTDEENT PHITQTKLDN GNGIQLPGSN GQQPSSDHEG QLIEEHGFRS PLAPTTAVPV
     RPGKFAPGRY PQERVDIELD TFPVQHGDFD GPYPHGLGPQ LNDSGVQEVA SHTTISWRPE
     LETTEYIISC HPIDHEEAPL QFRVPGTSSS ATLNGLTRGA TYNIVVEAQK GTDKHKVLEK
     RVTVGSPGSP EGVLQPVEDT CYDTFSGAHY SVGQEWERMS ESGFRLWCKC LGYGSGHFRC
     DSSKWCHDNG VNHRIGEKWD RRGENGQMMS CTCLGNGKGE FKCEPPEATC YDEGKMYNVG
     EQWQKEYLGA ICSCTCYGGQ QGWRCDNCRR PGAVSPDGTA GQTVSQFTQR YQQNYNLNCP
     IECYLPLGLQ ADTQHSQQTQ K
//
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error

file could not be opened "/ebi/srs/srs606/tmp/3VI821DDRMT/userpar.updat.tmp"
